30

Vulva

Blake Gilks

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Normal Anatomy

The vulva is composed of the following anatomic structures: mons pubis, clitoris, labia minora, labia majora, vulvar vestibule and vestibulovaginal bulbs, urethral meatus, hymen, Bartholin and Skene glands and ducts, and vaginal introitus.[1,2]

The *labia majora* are lined by keratinized skin containing all the cutaneous adnexa: hair follicles, sebaceous glands, apocrine glands, and sweat (eccrine) glands.[3] The *labia minora* are covered by nonkeratinized stratified squamous epithelium on their vestibular surfaces but have a thin keratinized layer on their lateral side. Skin adnexa are usually absent in them, but on occasion, one encounters both sweat and sebaceous glands.

The *Bartholin gland* is the major vestibular gland and has a tubuloalveolar structure. It is made up of acini composed of mucus-secreting columnar cells and a duct lined with transitional epithelium.[4] *Minor vestibular glands* are of simple tubular type and are lined with a mucus-secreting columnar epithelium that merges with the stratified squamous epithelium of the vestibule.

Skene or *periurethral glands* are analogous to the male prostate gland; they are lined by a pseudostratified mucus-secreting columnar epithelium that merges with the transitional-type epithelium of the ducts, which in turn joins with the stratified squamous epithelium of the vestibule.

The *hymen* is lined by nonkeratinized stratified squamous epithelium on both surfaces.

The *clitoris* contains erectile tissue similar to that present in the corpora cavernosa of the penis.

Most of the vulvar lymph vessels drain to the superficial inguinal nodes, but those in the clitoris empty directly into the deep chain.

Mammary-Like Glands of the Vulva and Related Lesions

Mammary-like glands of the vulva, formerly thought to be ectopic breast tissue related to the "milk line," are now recognized as a normal finding in the vulva,[5] and are found primarily in the sulcus between the labium minus and labium majus. These glands consist of ducts, variably with associated acini, lined by glandular epithelium identical to that of the breast. The ducts draining these glands empty through the skin. Clear cells (Toker cells) may be found singly or in clusters where these ducts traverse the epidermis. This tissue is subject to many of the physiologic and pathologic changes that occur in the normally situated breast and some that seem peculiar to this location. These include swelling and secretion of milk during pregnancy, cysts,[6] peculiar hyperplastic changes,[7] so-called pseudoangiomatous stromal hyperplasia (PASH; see Chapter 36),[8] fibroadenoma (including the juvenile type),[8–10] (Fig. 30.1) phyllodes tumor,[11,12] and carcinoma.[6,13–15] Most of the latter have been of ductal type, but any histotype/molecular subtype, i.e. luminal, basal-like, HER2, may be encountered.[16–18] In addition, it is likely that ectopic mammary tissue is the source of the common benign vulvar tumor known as papillary hidradenoma.

Abstract

Vulvar pathology encompasses a wide range of inflammatory and neoplastic conditions. Although generalized dermatopathies can involve the vulvar skin, we will focus on those specific conditions that involve the vulva preferentially or exclusively. Most neoplasms of the vulva arise from the squamous epithelium; unlike squamous cell neoplasia of sun-exposed skin, vulvar squamous cell carcinoma can metastasize and is associated with significant mortality. Vulvar squamous carcinoma can arise from human papilloma virus (HPV)–independent or HPV-associated pathways, and these differ with respect to age at onset, molecular events during pathogenesis, risk factors, precursor lesions, and prognosis. Neoplasms other than squamous cell carcinoma can arise from specialized epithelia (e.g., Bartholin gland or mammary-like glands of the vulva) or hormone receptor–expressing mesenchymal cells of the vulva.

Keywords

Vulva, VIN,
lichenoid inflammation,
lichen sclerosus,
squamous cell carcinoma,
HPV

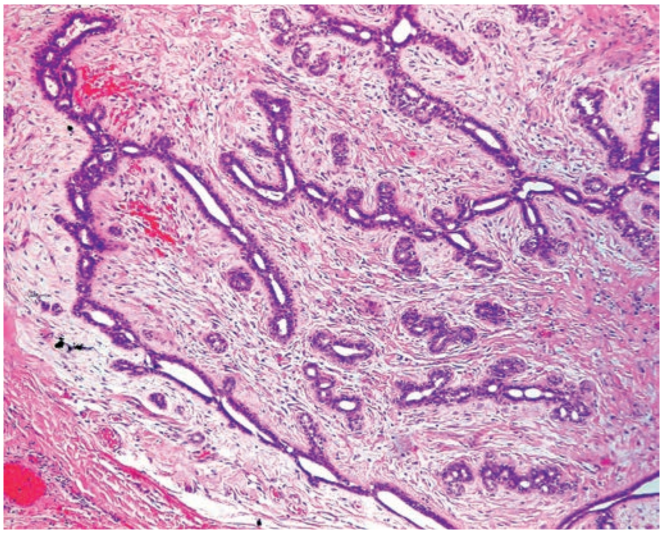

Figure 30.1 Fibroadenoma of vulva arising from ectopic breast tissue.

Inflammatory Diseases

Syphilis in women often manifests itself initially in the vulvar region. The fully developed syphilitic chancre is composed microscopically of plasma cells, lymphocytes, and histiocytes, and is covered by a zone of ulceration infiltrated by neutrophils and necrotic debris. The microscopic appearance is not specific, but the combination of numerous plasma cells and endarteritis should alert to the diagnosis. Your diagnostic report can suggest the possibility of syphilis, based on the histopathologic findings, indicating to the clinician the need to exclude this possibility with appropriate serologic testing on the patient. Additionally, immunostains for *Treponema pallidum* are now available and allow for easy confirmation of the causative organisms.[19] Sometimes, the possibility of syphilis is first suggested on the basis of the microscopic examination of an enlarged inguinal lymph node if this node shows a combination of capsular and pericapsular fibrosis, follicular hyperplasia, plasma cell infiltration, and endarteritis. The latter feature, which represents the most useful clue to the diagnosis, is particularly well seen in or outside the nodal capsule (see Chapter 37).

Granuloma inguinale (donovanosis) is a chronic infection caused by *Klebsiella* (*Calymmatobacterium*) *granulomatis*, a gram-negative, nonmotile, encapsulated bacillus.[20–22] It begins as a soft elevated granulomatous area that enlarges very slowly by peripheral extension and ulcerates. Microscopically, there is a dense dermal inflammatory infiltrate composed of histiocytes and plasma cells, with a scattering of small abscesses.[23] The diagnosis rests on the demonstration of Donovan bodies, which appear as small round encapsulated bodies inside the cytoplasm of the histiocytes. They can be seen in hematoxylin-eosin (H&E) sections but are best demonstrated with Giemsa or Warthin-Starry stains. Pronounced pseudoepitheliomatous hyperplasia, which may accompany chronic lesions, should be distinguished from the very rare squamous cell carcinoma that may arise in such areas.[24] The infection can spread to the retroperitoneum and simulate a soft tissue neoplasm.[25]

Lymphogranuloma venereum (LGV) is a venereal disease produced by *Chlamydia trachomatis* organisms (specifically L-serovars).[26–28] It mainly affects lymph vessels and lymphoid tissue. The initial small ulcer at a site of venereal contact often goes unnoticed. The first clinical manifestation is swelling of inguinal lymph nodes caused by stellate abscesses surrounded by pale epithelioid cells.[29] There is extensive scarring as the disease progresses, often leading to fistulas and strictures of the urethra, vagina, and rectum. It is increasing in incidence, especially in homosexual men.[30] The diagnosis can be confirmed by submission of swabs for nucleic acid amplification, with LGV genotyping on samples positive for *Chlamydia*.[30] Rainey[31] reported 11 cases of squamous cell carcinoma or adenocarcinoma arising from lymphogranulomatous strictures. Most of the tumors were located in the anorectal area.

Crohn disease can involve the vulvar region.[32–35] In some cases, the vulvar lesions are associated with perineal disease and fistula formation, whereas in others they are separated from the anal lesions by normal tissue. Grossly, erythematous areas appear that later ulcerate. Microscopically, noncaseating granulomas may be found. The process reported as *vulvitis granulomatosa* is probably related to Crohn disease, in that some of the patients have subsequently developed either intestinal Crohn disease or cheilitis granulomatosa.[36]

Behçet disease can, rarely, involve the vulvar region, where it presents as a microscopically nonspecific ulceration.[37,38]

Necrotizing fasciitis of the vulva may be seen in diabetic women. It is associated with a high mortality rate; wide excision of the diseased tissue is the treatment of choice.[39]

Vulvar vestibulitis is a disorder characterized microscopically by a nonspecific chronic inflammatory infiltrate predominantly involving the mucosal lamina propria and the periglandular/periductal connective tissue of the vestibular region.[40] It is unrelated to human papilloma virus (HPV).[41]

Plasma cell vulvitis (of Zoon) is an uncommon condition of uncertain etiology. It typically presents as a solitary, asymptomatic, sharply defined red/brown patch. Microscopically, there is a dense band-like mononuclear inflammatory infiltrate in the superficial dermis, consisting predominantly (>50%) of plasma cells.[42] The differential diagnosis includes secondary syphilis and lichenoid drug reaction, but neither of these conditions present as a solitary lesion resembling those of plasma cell vulvitis.

Spongiotic and Lichenoid Reactions of the Vulvar Skin

There exists a group of vulvar diseases that are pathogenetically unrelated but that have several features in common at the clinical level. They typically present as a long-standing lesion consisting of irregular areas of thickened skin, often accompanied by severe pruritus. The color is usually white, in which case the clinically descriptive term *leukoplakia* has been used (note that this is not an acceptable histopathologic diagnosis!). In other instances, the lesions are red or a mixture of both colors. They are easily traumatized and excoriated. In some of these lesions the vulvar soft tissues are atrophied and shrunken, in which case the clinical term *kraurosis vulvae* has been employed.

In the presence of a lesion with some of these clinical features, it is essential to reach a specific diagnosis, and this often necessitates the performance of a biopsy.[43] Multiple biopsies may be necessary if the lesion is large or varies in appearance from place to place. Although a key function of the biopsy is to exclude neoplasia, it is important to reach a specific diagnosis as this will guide subsequent management, and the former practice of diagnosing benign "vulvar dystrophy" or "squamous hyperplasia" is not acceptable.[44,45] What follows is a list of the most commonly encountered inflammatory conditions of the vulva; this list is by no means exhaustive but will be sufficient to handle most vulvar biopsies taken for a non-neoplastic inflammatory process that will be encountered in general surgical pathology practice, focusing on those entities that chiefly involve the vulva. The vulvar skin can be secondarily involved in a wide range of inflammatory dermatopathies and the reader is referred to Chapter 2 for a full discussion of these conditions.

Spongiotic dermatitis (eczematous reaction) is a nonspecific pattern of cutaneous inflammation, familiar to those whose practice includes a significant dermatopathology component. It is characterized histologically by intercellular edema in the epidermis (spongiosis) with intraepithelial lymphocytes, and less commonly neutrophils and/or eosinophils. Pure acute spongiotic reactions are rarely encountered in vulvar biopsies, but spongiotic dermatitis is not uncommonly seen admixed with a chronic process, especially lichen simplex chronicus (discussed below), so awareness of the histopathologic features is important. Eczematous reactions confined to the vulva are most commonly attributable to allergic or irritant contact reactions, with drug reaction and atopic reaction less common. In patients with allergic contact reaction, the precipitant may be difficult to identify, clinically, as the reaction can persist for variable periods of time after removal of the irritant. Management consists of scrupulous avoidance of irritants/allergens.[46] When longstanding, there is progression to lichen simplex chronicus and it is our impression that many cases of lichen simplex chronicus start as an acute spongiotic dermatitis.

Lichen simplex chronicus is probably the most common diagnosis rendered on vulvar biopsies. It can affect nonvulvar sites or be limited to the vulva, where it manifests as pruritic scaly plaques.[46] The microscopic findings reflect chronic irritation, and the diagnosis of lichen simplex chronicus does not indicate a single disease entity but instead reflects chronic irritation of vulvar skin from any cause. On histopathologic examination there is hyperkeratosis (predominantly orthokeratosis, with parakeratosis focally present, for example, as sites of excoriation) with epidermal hyperplasia and a patchy, predominantly lymphocytic inflammatory infiltrate in the superficial dermis (Fig. 30.2). Because lichen simplex chronicus reflects trauma, and can appear secondary to many different primary dermatopathic conditions, it is important to search for an underlying disease process that has precipitated the lichen simplex chronicus. That being said, in most cases no underlying condition can be identified. Cutaneous fungal infections can result in changes of lichen simplex chronicus but can be ruled out with periodic acid–Schiff–diastase (PAS-D) stain. The differential diagnosis of lichen simplex chronicus, especially for the clinician, is vulvar intraepithelial neoplasia (VIN), but lichen simplex chronicus lacks the atypia of VIN (differential diagnosis discussed in more detail later, in the section on differentiated VIN [dVIN]).

Lichen planus is an idiopathic inflammatory dermatopathy characterized by pruritic red/purple papules.[46] While there is usually extragenital involvement, vulvar lesions may be the only finding at presentation. The lesions resolve after 12–18 months in most patients. The histopathologic findings are a band-like infiltrate in the superficial dermis, with damage to basal keratinocytes, resulting in apoptotic keratinocytes (Civatte bodies). The inflammatory infiltrate does not extend into the suprabasal keratinocytes. Hyperkeratosis with wedge-shaped hypergranulosis is a common finding. Lichen planus is considerably less common than lichen simplex chronicus or lichen sclerosus. The absence of basal keratinocyte degenerative changes aids in the distinction of lichen simplex chronicus from lichen planus. Lichen planus involves mucosal membranes and other extragenital sites, which is a clinical finding that can also serve to distinguish lichen planus from lichen sclerosus. The histopathologic features useful in differential diagnosis between lichen planus and lichen sclerosus are discussed in the following paragraphs.

Lichen sclerosus (also spelled sclerosis) of the vulva may occur in any age group, including children (Fig. 30.3).[47] In the latter group, the vulvar region represents the most common location, and there is a high incidence of spontaneous involution at the time of puberty.[48] The microscopic features are similar but not identical to those seen in this disorder when it occurs elsewhere in the skin (see Chapter 2) (Fig. 30.4). It has been stated that the minimal histologic criteria for the microscopic diagnosis of lichen sclerosus (LS) are the presence

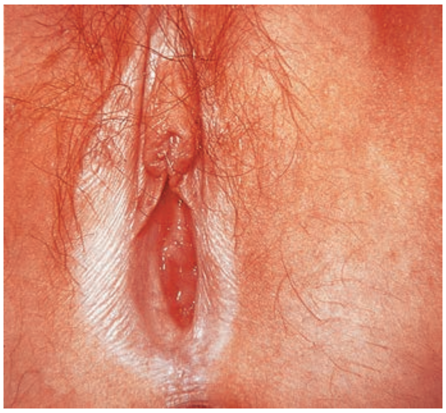
Figure 30.3 Clinical appearance of vulvar lichen sclerosus.

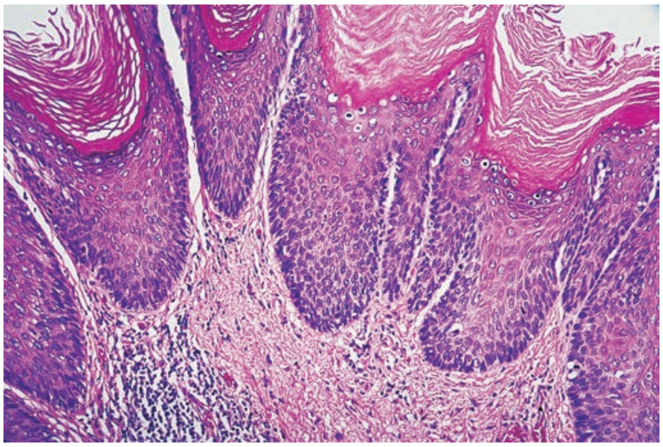
Figure 30.2 Lichen simplex chronicus, with hyperkeratosis, epidermal hyperplasia, and chronic inflammation of the underlying stroma. There is no significant atypia.

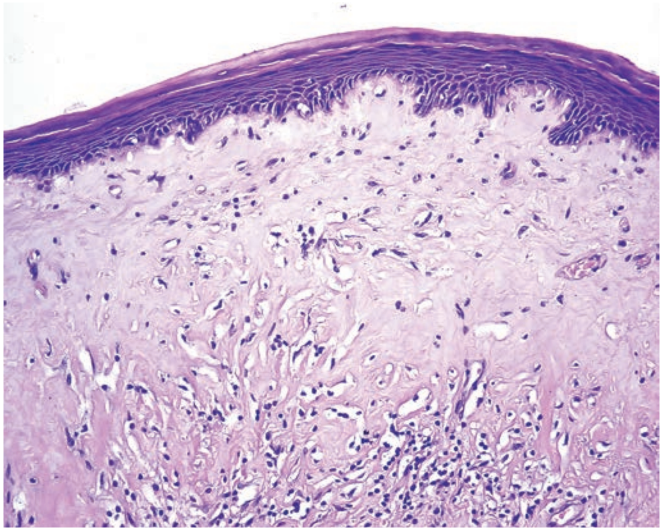
Figure 30.4 Lichen sclerosus of vulva. A thick hypocellular edematous layer is bounded by atrophic epidermis on one side and inflamed stroma on the other.

of a vacuolar interface reaction pattern in conjunction with dermal sclerosis (homogenized and hyalinized eosinophilic collagen bundles) of any thickness in between the inflammatory infiltrate and the epithelium and/or vessel walls.[49] In the early stages, LS may be difficult to diagnose as it may be indistinguishable from lichen planus.[50] In such cases, the differential diagnosis should be noted, and it can be indicated in the pathology report that with follow-up it will declare itself to be either lichen planus or LS, as in LS the pathognomonic superficial hyalinized collagen will appear. The diagnostic alterations of early LS may be very subtle and often are more prominent in adnexal structures than in the interfollicular skin.[51] The overlying epidermis is characteristically atrophic, but on occasion it may show foci of hyperplasia[52]; however, the presence of hyperplasia in LS, especially as a focal finding, forming a clinically recognizable discrete lesion with an abrupt change from the adjacent atrophic epithelium, should always raise the differential diagnosis of dVIN arising in LS. The presence of basal atypia and altered maturation (loss of the granular cell layer) in the hyperplastic focus is evidence supporting a diagnosis of dVIN.

It is now accepted that LS is a precancerous condition, associated with an increased risk of developing dVIN and HPV-independent squamous cell carcinoma. The risk, however, is relatively small. In one series, squamous cell carcinoma developed in only one of 92 patients,[53] and in another it was found in 12 (4%) of 290 patients followed for a mean period of 12.5 years.[54] In a large (n = 507) prospective study of patients with LS, 0 of 357 patients who were compliant with treatment recommendations developed invasive squamous cell carcinoma or VIN, compared to 7 of 150 patients who were not fully compliant.[55] While many invasive HPV-independent vulvar squamous cell carcinomas are seen in a background of LS at the time of diagnosis, newly diagnosed LS (in the absence of neoplasia) can be managed medically with a relatively low risk of progression. The designation "atypical LS" has been used for cases of LS where there is basal atypia of the atrophic epithelium, greater than would be expected in usual LS.[56] Atypical LS has been reported to show overexpression of p53,[56,57] and atypical LS may well be a step in the pathway towards development of dVIN, but we do not have the ability to render the diagnosis of atypical LS reproducibly, nor do we understand its clinical significance; therefore, it cannot be considered to be a robust clinically relevant diagnosis. In practice, the presence of basal atypia in LS should be documented in the Comment field of the surgical pathology diagnostic report, indicating that it may be associated with increased likelihood of malignant transformation, with recommendation for close follow-up.

Human Papilloma Virus and Vulvar Pathology

The role of HPV in vulvar pathology is analogous to the one it plays in the vagina and cervix, and is discussed in detail in connection with the latter (see Chapter 32). In the vulva, this includes condyloma (acuminatum and flat), as well as high-grade squamous intraepithelial lesion (HSIL) VIN2/3 and HPV-associated invasive squamous cell carcinoma. The vulva differs from the cervix in that there are a significant number of HPV-independent squamous cell carcinomas, unlike in cervix, where virtually all squamous cell carcinomas are HPV-associated. It is becoming apparent that the HPV-independent intraepithelial and invasive squamous cell neoplasms are more aggressive than their HPV-associated counterparts in the vulva.[58–60] Accordingly, attention will be paid to the differences (histopathologic and natural history) between these two subtypes of vulvar squamous neoplasia, which are summarized in Table 30.1. With respect to diagnosis, immunostaining for p16INK4a has emerged as a sensitive and specific surrogate for detection of HPV-associated versus HPV-independent vulvar squamous neoplasia, with sensitivity of 100% and specificity of 98%–99%.[61,62] Staining is most reliably performed on intraepithelial lesions or early invasive carcinomas, as p16 expression can be lost during tumor progression. Polymerase chain reaction (PCR) for HPV DNA allows for viral genotyping and is highly sensitive, but lacks specificity.[60] In situ hybridization for HPV is highly specific, but is more expensive than immunostaining and has a longer turnaround time; however, it can be valuable in establishing HPV status for those cases where the clinical, histomorphologic, and p16 immunostaining data are not concordant.[62] Detection of mRNA of HPV oncogene E6 can be used to establish an etiologic role for HPV by demonstrating that the virus genome is being transcribed. However, such testing is not widely available, and p16 immunostaining is currently the most important surrogate test of HPV status.

Table 30.1 Human Papilloma Virus-dependent and Human Papilloma Virus-independent Vulvar Intraepithelial Neoplasia and Vulvar Squamous Cell Carcinoma

	HPV-ASSOCIATED	HPV-INDEPENDENT
Prevalence in VIN without invasive carcinoma	87%	13%
Prevalence in invasive squamous cell carcinoma	29%	71%
Age (peak incidence)	Sixth decade	Eighth decade
Histologic features of precursor	HSIL (VIN2/3)	Differentiated VIN (dVIN)
Histologic type of invasive carcinoma	Warty/basaloid	Well-differentiated keratinizing
Lichen sclerosus	Generally absent	Often present
Nonsurgical treatment of VIN	Imiquimod and other antiviral/immunomodulatory treatments effective	No role for antiviral treatment
Survival/prognosis	Less aggressive	Significantly higher recurrence rates and mortality

dVIN, Differentiated vulvar intraepithelial neoplasia; *HPV*, human papilloma virus; *HSIL*, high-grade squamous intraepithelial lesion; *VIN*, vulvar intraepithelial neoplasia.

Condyloma and Seborrheic Keratosis

Vulvar **condyloma** is a venereal disease caused by HPV, usually type 6. Although according to the 2012 Lower Anogenital Squamous Terminology (LAST) recommendations, these lesions should be diagnosed as (VIN1) (low-grade squamous intraepithelial lesion [LSIL]),[63] the diagnosis of condyloma is well established, while a diagnosis of LSIL may lead to confusion. The diagnosis of VIN1 was not used for vulvar lesions for the 8 years prior to the LAST recommendations, as the 2004 International Society for the Study of Vulvar Diseases had dropped it from recommended terminology as it was generally accepted to not have a specific meaning. It was instead viewed as a collection of different conditions, including low-risk HPV infection.[64] While we are able to endorse LSIL (CIN1) for cervical

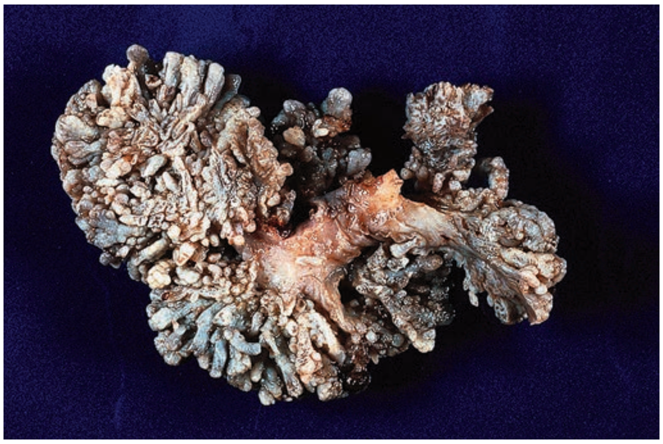

Figure 30.5 Large condyloma of vulva.

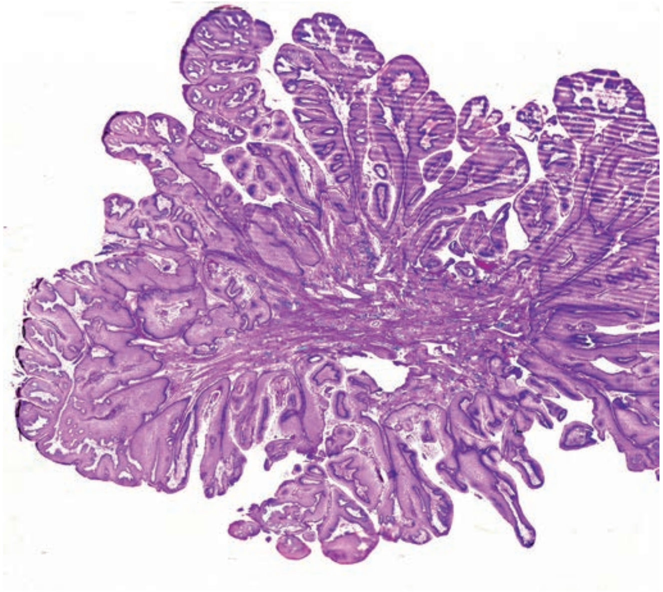

Figure 30.6 Whole mount of condyloma acuminatum of vulva.

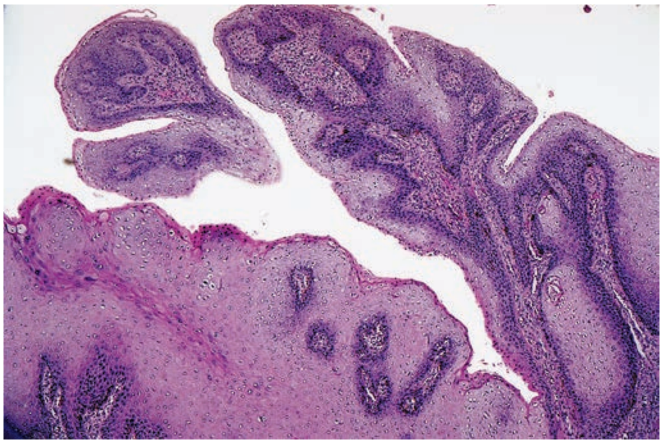

Figure 30.7 Papillomatous shape of vulvar condyloma.

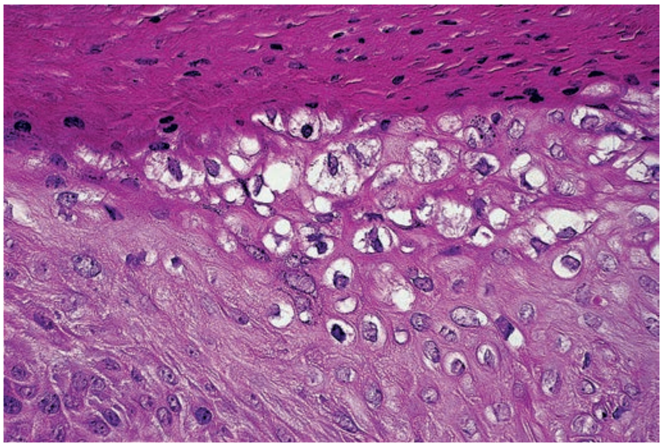

Figure 30.8 Prominent koilocytotic changes in vulvar epithelium.

lesions, we do not recommend adopting this terminology for condylomatous vulvar lesions, and recommend, instead, the diagnosis of "condyloma." The better-known form of condyloma is **condyloma acuminatum,** which is characterized grossly by one or several soft elevated masses of variable size (Fig. 30.5). Microscopically there is a complicated papillary arrangement of well-differentiated undulating squamous epithelium supported by delicate, well-vascularized connective tissue stalks containing mononuclear inflammatory cells (mainly CD4+ and CD8+ cells) (Figs. 30.6 and 30.7).[65] The other form of condyloma, which is actually much more common, is the **flat condyloma** (not to be confused with the *condyloma latum* of syphilis). The cytologic features are similar in both forms. Koilocytosis of the malpighian epithelium and lymphocytic infiltration of the stroma are regular features (Fig. 30.8). Koilocytosis refers to the combination of perinuclear cytoplasmic clearing and wrinkling of the nuclear membrane (nuclear "raisins"). As a rule, this change is not as florid in vulvar condylomas as it tends to be in condylomas of the cervix. A typical condyloma shows minimal basal or parabasal cell atypia, orderly maturation, and a smooth transition to koilocytotic intermediate and superficial cells; mitoses may be numerous but are all typical.[66,67] In contrast, the lesions of VIN2/3 exhibit abnormal mitoses and nuclear pleomorphism, enlargement, and hyperchromasia in the basal and parabasal cell layers, as well as "block positivity" on p16 immunostaining, with strong nuclear and cytoplasmic immunoreactivity in all cells of at least the basal third of the epithelium, but with positivity usually extending into the upper half (see later section). The increased proliferative activity of condyloma (in contrast to fibroepithelial polyp and squamous papilloma) can be easily appreciated with the Ki-67 stain.[68] The DNA content of condylomas is diploid and polyploid (including tetraploidy and octaploidy), in contrast to the aneuploid pattern seen in most cases of VIN2/3.[69]

Sometimes one sees verrucopapillary vulvar lesions that lack the viral cytopathic effects (koilocytic change) of condyloma; these are often referred to as *squamous papillomas* and usually contain genital HPV types by PCR.[70] Conversely, there may be multinucleated atypia of the epithelial squamous cells associated with reactive conditions in the absence of HPV infection.[71] A final consideration in the diagnosis of condyloma in children is that verruca vulgaris, due to HPV2, can occur on the vulva of children and be morphologically indistinguishable from condyloma.[72] It is therefore important to exercise caution in diagnosing condyloma in children (with the implication of a venereal infection/sexual abuse). We recommend that HPV testing to document genital-type HPV be required to support a diagnosis of condyloma in this setting. Another vulvar lesion which needs to be discussed here is the process morphologically indistinguishable from cutaneous seborrheic keratosis, which in this particular location is usually associated with HPV infection.[73] The differential diagnosis of condyloma also includes a lesion characterized by *epidermolytic hyperkeratosis*, which could be related to Darier disease or represent a form of Hailey–Hailey disease.[74] The acantholysis is usually suprabasal, but we have also seen it at the level of the granular layer. A final important differential diagnosis is verrucous carcinoma. Despite the name, verrucous carcinoma is not associated with HPV and is part of the spectrum of non-HPV-associated vulvar squamous neoplasia; it is distinguished from condyloma by examination of the epidermal/dermal junction. Verrucous carcinoma is characterized by a distinctive pattern of bulbous downgrowths with pushing margins, and will be discussed in greater detail later in this chapter.

The traditional therapy for condyloma consisted of podophyllin application. Microscopically, this results in epidermal pallor, necrosis of keratinocytes, and marked increase in mitosis; these changes wane after 72 hours and are essentially gone in 1 week.[75] Occasionally, similar microscopic changes are seen in the absence of podophyllin therapy.[76] The treatment of choice for these lesions at present is carbon dioxide laser.[77]

Squamous Intraepithelial Lesions

It is now appreciated that squamous neoplasia of the vulva can be subclassified into HPV-associated and HPV-independent forms, which differ with respect to etiology, age at diagnosis, natural history, and morphology (i.e., they are different diseases). These differences are summarized in Table 30.1. In North America, most preinvasive lesions (VIN) are HPV-associated (HSIL) (VIN2/3) rather than dVIN, while most invasive squamous cell carcinomas are HPV-independent; this is thought to reflect the more rapid progression of dVIN to invasive carcinoma.[60] The presence of an admixture of HPV-associated and HPV-independent squamous neoplasia in the vulva is in contrast to the uterine cervix or vagina, where virtually all squamous neoplasia is HPV-associated. Because of the histopathologic differences between HPV-associated and HPV-independent squamous neoplasia (both intraepithelial and invasive), they will be considered separately in the following sections. It is important to acknowledge that clinical and morphologic features (based on examination of H&E stained slides) cannot distinguish between HPV-associated and HPV-independent squamous neoplasia in every case; however p16 immunostaining is a sensitive (100%) and specific (>98%) marker of HPV-associated squamous neoplasia in the vulva.[61,62] Interpretation of p16 immunostaining, as for cervical lesions, is based on the presence or absence of "block" positivity, defined as intense nuclear and cytoplasmic staining of *every* cell in the basal third of the epithelium (Fig. 30.9). p16 positivity, so defined, is evidence of HPV-associated VIN or invasive squamous cell carcinoma. Note that p16 staining intensity often decreases in the superficial layers of HSIL (VIN2/3), as the neoplastic squamous epithelium undergoes maturation.

Human Papilloma Virus-Associated Squamous Intraepithelial Neoplasia: High-Grade Squamous Intraepithelial Lesion (VIN2/3)

The in situ or pre-invasive lesion of HPV-associated vulvar squamous neoplasia is, as noted previously, referred to as HSIL or high-grade vulvar intraepithelial neoplasia (VIN2/3) and is entirely analogous to equivalent lesions in the vagina (VaIN2/3), cervix (CIN2/3), or anal mucosa (AIN2/3).[63] The recommended terminology for preinvasive lesions associated with oncogenic HPV (most commonly HPV16 or 18, but a number of other oncogenic HPV genotypes have also been reported), according to the LAST recommendations, is HSIL (VIN2 or VIN3).[63] In practice, it is not possible to reproducibly distinguish between VIN2 and VIN3, nor is the distinction clinically relevant. It has been proposed that VIN2 be used for cases where the "dysplasia" does not extend into the upper third of the squamous epithelium, while VIN3 be diagnosed in cases with full-thickness or near-full-thickness dysplasia; biologically this is a curious proposition, as all cells in VIN2/3 are neoplastic and transformed by oncogenic HPV (i.e., the full thickness of the epithelium is replaced by a clonal neoplastic proliferation, irrespective of whether there is some degree of flattening or maturation of the superficial cells). Any distinction between VIN2 and VIN3, accordingly, is arbitrary, and one may simply call all such cases VIN3 or VIN2/3, in practice. If this seems a touch iconoclastic, it is worth noting that according to the 2004 recommendations of the International Society for the Study of Vulvovaginal Disease, the diagnosis of "high-grade VIN" was used for all lesions that would be diagnosed as VIN2 or VIN3 according to the LAST criteria,[64] and many of us used this simplified system for almost a decade and found it entirely satisfactory.

HSIL (VIN2/3) usually presents as a slightly elevated, plaque-like lesion with a red velvety appearance.[78] It is typically centered in the labia majora, and it may extend to the perineum and anus. Microscopically, there is hyperkeratosis and parakeratosis, acanthosis, and a variable number of multinucleated dyskeratotic cells and abnormal mitoses involving the entire thickness of the epidermis (Fig. 30.10). The acrotrichium (intraepidermal portion of the hair follicle) is often involved, whereas the acrosyringium (intraepidermal portion of the sweat gland) is usually spared.[79,80] On occasion, the tumor cells are arranged in a nested pattern and/or have a clear cytoplasm, thus simulating Paget disease.[81,82] The lesions of HSIL (VIN2/3) may be uniformly composed of cells with high N:C ratio (basaloid pattern VIN2/3) or there may be maturation as the cells move toward the

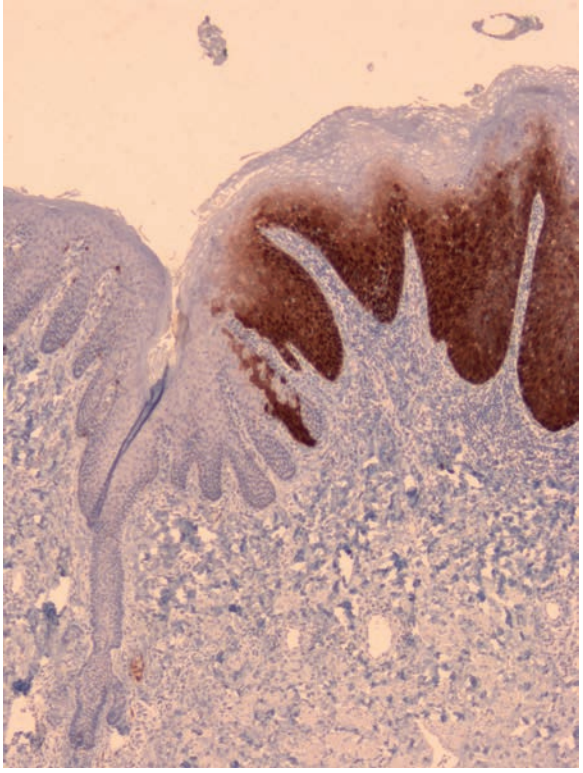

Figure 30.9 "Block" immunoreactivity for p16, with strong nuclear and cytoplasmic staining of all cells of at least the basal third of the epithelium, in HSIL (VIN2/3), as a surrogate test for the presence of oncogenic HPV.

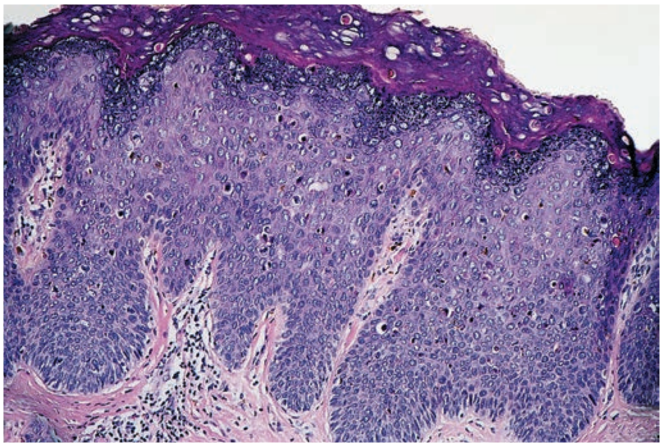

Figure 30.10 Typical microscopic appearance of HSIL (VIN2/3).

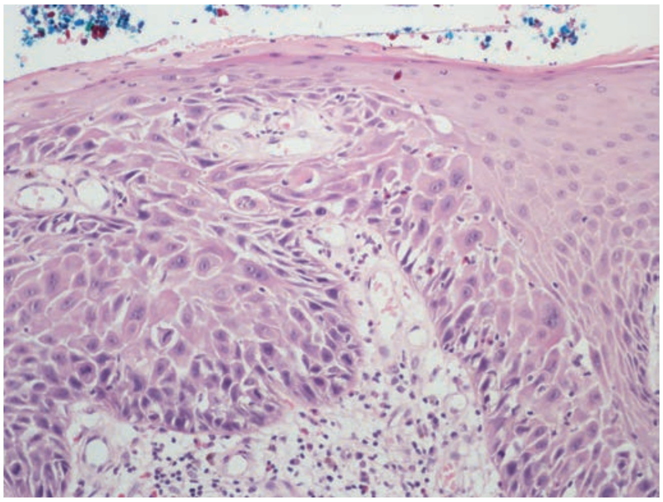

Figure 30.11 Differentiated VIN (dVIN), showing basal epithelial atypia.

surface, with epithelial hyperplasia and koilocytic change (warty pattern VIN2/3). This latter pattern can mimic condyloma but shows greater atypia, as well as block p16 positivity.

The type of HSIL (VIN2/3) that was, historically, designated as *bowenoid papulosis* presents as multiple, often pigmented, papules in or near the vulva of young patients. Clinically, they resemble verrucae, small condylomas, or nevi, but microscopically they show striking cytologic atypia, similar to that of Bowen disease/usual HSIL.[83] It is important to note that the terms Bowen disease and Bowenoid papulosis may be used clinically but the pathologic diagnosis is HSIL (VIN2/3) for both, as there are no histopathologic features for reliably distinguishing between them. The designations of "warty" or "basaloid" VIN similarly are not routinely used in practice, as they are not of clinical significance.

It has been stated that, if left untreated, HSIL (VIN2/3) will progress into invasive carcinoma in approximately 10% of cases, but the rate of transformation varies widely among the different series.[84] The therapy for HSIL (VIN2/3) depends on the age of the patient and the size, configuration, and distribution of the lesions.[84] Localized lesions can be treated by wide local excision, skinning vulvectomy, laser, or topical therapy.[85] Imiquimod, an immune-response modulator, can be used to treat HSIL (VIN2/3), with many lesions showing a response, sometimes a complete response.[86]

It is anticipated that with increasingly widespread use of vaccination against HPV, cases of HSIL (VIN2/3) will start to decrease in the coming years. It has been increasing, especially in younger women. The frequent history of an abnormal cervical smear is important, and all patients with a past history of HSIL or HPV-associated squamous cell carcinoma elsewhere in the lower anogenital tract are at increased risk for vulvar disease.

Human Papilloma Virus-Independent Squamous Intraepithelial Neoplasia: Differentiated Vulvar Intraepithelial Neoplasia

VIN of differentiated type (dVIN) is consistently negative for HPV, arises in elderly women, is frequently associated with squamous hyperplasia and LS, and is related to invasive squamous cell carcinoma of keratinizing type.[56,87–89] Microscopically, it is characterized by (1) epidermal hyperplasia with parakeratosis and elongated and anastomosing rete ridges, (2) significant basal cytologic atypia, and (3) cells with abundant eosinophilic cytoplasm (Fig. 30.11).[89] It is increasingly appreciated that dVIN is under-recognized in clinical practice, as the aforementioned changes may not all be present or may be subtle.[90,91] Immunostaining is of limited use as a diagnostic adjunct, as Ki-67 staining intensity overlaps with that of reactive conditions in the differential diagnosis, and there is a variable pattern of p53 expression; while some cases show complete loss or convincing overexpression of p53, consistent with underlying *TP53* mutations, this is not a consistent finding.[89,92–94] p16 immunostaining is consistently negative (i.e., lacking the block positivity associated with oncogenic HPV-associated VIN). It is important to note that HPV-independent VIN may be higher grade and may even mimic the basaloid pattern seen in HSIL (VIN2/3).[95] This variant of HPV-independent VIN can be distinguished from HPV-associated HSIL (VIN2/3) by p16 immunostaining; as well, it typically shows abnormal p53 immunoreactivity (complete absence or strong diffuse positivity), in our experience. What to call such a lesion is another matter, as it is not adequately addressed in current classification systems. Poorly differentiated dVIN presents itself as a potential designation (to join other oxymoronic diagnoses such as large cell variant of small cell carcinoma or oxyphilic variant of clear cell carcinoma), but it may be preferable to simply diagnose it as an HPV-independent high-grade squamous intraepithelial lesion and explain the unconventional terminology in the comment field of your report. dVIN is infrequently diagnosed in the absence of invasive squamous cell carcinoma, suggesting that it progresses rapidly to invasion. This view is supported by a small case series of dVIN without invasive carcinoma, where most patients developed invasive carcinoma, with a median interval between diagnosis of dVIN and invasive carcinoma of 1.9 years, a significantly worse outcome than for HSIL (VIN2/3).[60]

Vulvar acanthosis with altered differentiation (VAAD) is characterized by marked acanthosis, a variable verruciform architecture, loss of the granular layer, cytoplasmic pallor at the surface, and multilayered parakeratosis. It has been suggested that VAAD (which is consistently negative for HPV) may be a precursor or a risk factor for verrucous carcinoma.[96]

Invasive Squamous Cell Carcinoma

General Features

Squamous cell carcinoma accounts for approximately 95% of the malignant tumors of this organ.

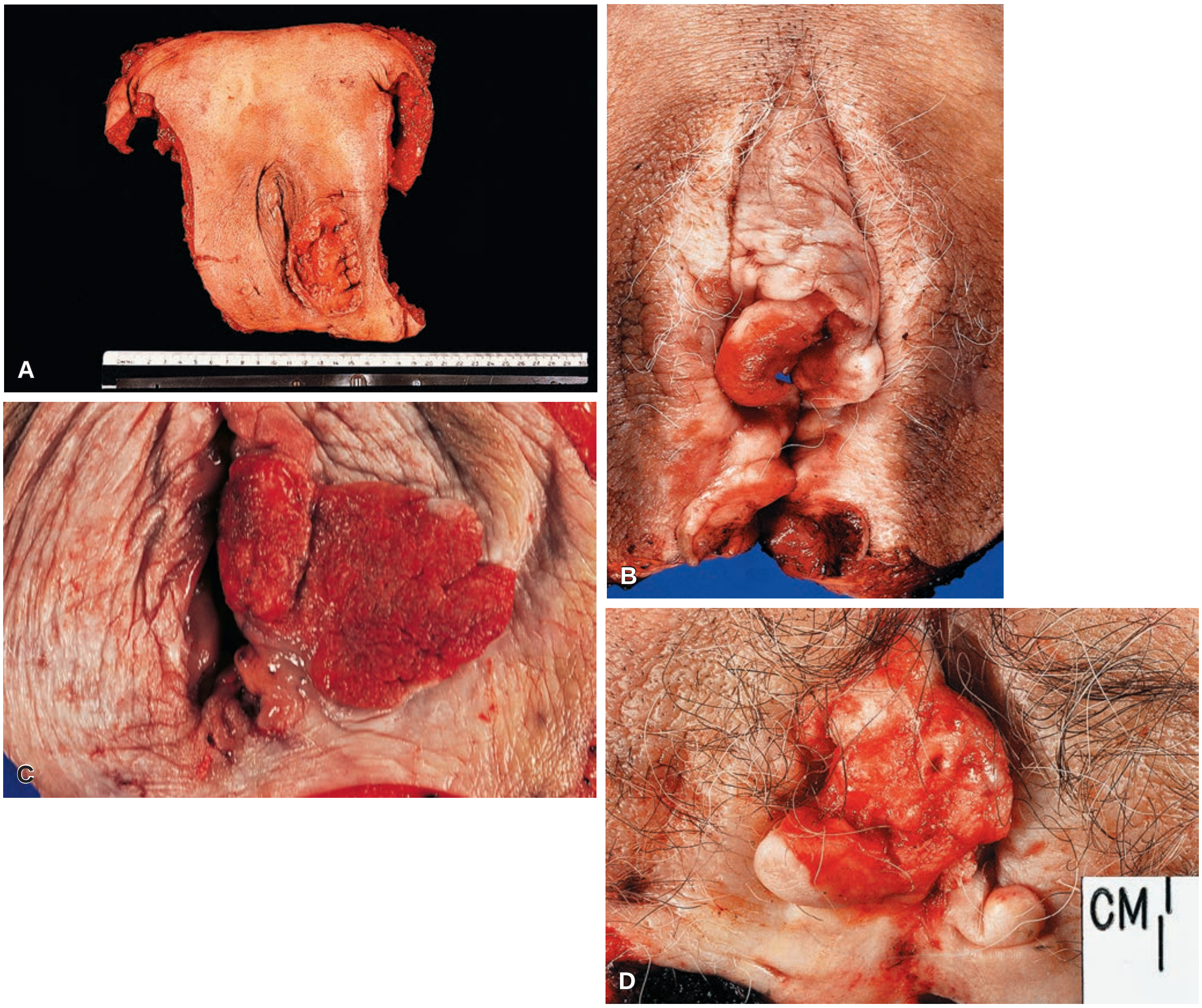

Figure 30.12 **Gross Appearance of Invasive Squamous Cell Carcinoma of Vulva. A**, Tumor of labium majus. **B**, Tumor of clitoris. **C**, Tumor involving both labia. **D**, Huge tumor mass involving all vulvar structures.

Invasive squamous cell carcinoma of the vulva arises most commonly on the labia majora but may be found on the labia minora or in the region of the clitoris (Fig. 30.12).[97] The immunohistochemical features of vulvar squamous cell carcinoma are not distinctive.

Human Papilloma Virus-Associated Invasive Squamous Cell Carcinoma

HPV-associated invasive squamous cell carcinomas are less common than HPV-independent carcinomas of the vulva.[98,99] Patients with HPV-associated disease are, on average, a decade or more younger than those with HPV-independent tumors, and they often have a history of prior cervical cytology abnormality, cervical intraepithelial neoplasia (CIN), or cervical carcinoma. It is curious that the vulvar squamous cell carcinomas that develop after a successfully treated cervical squamous cell carcinoma appear to be derived from the same malignant clone, but behave more like an independent primary vulvar carcinoma than a metastasis.[100] HPV-associated squamous cell carcinomas are more common in patients who are immunocompromised. Morphologically, most HPV-associated carcinomas are of basaloid or warty pattern (Fig. 30.13); however a significant minority are well or moderately differentiated keratinizing carcinomas,[62] and thus are morphologically indistinguishable from HPV-independent carcinomas. Warty-pattern carcinoma[101] should not be confused with verrucous carcinoma, despite the fact that the gross appearance of the latter has sometimes been described as "warty." The term "warty pattern carcinoma," if used at all, should be reserved for the squamous cell carcinomas in which the tumor cells display marked pleomorphism, enlargement, atypia, and multinucleation. These features are often associated with koilocytotic atypia in the adjacent epithelium. Basaloid-pattern carcinoma[101] has an appearance analogous to its counterpart in the upper aerodigestive tract and penis. Peripheral palisading is prominent (see Fig. 30.13). Typical HSIL (VIN2/3) may be found adjacent to the invasive carcinoma, and is strong evidence that the carcinoma is HPV-associated.

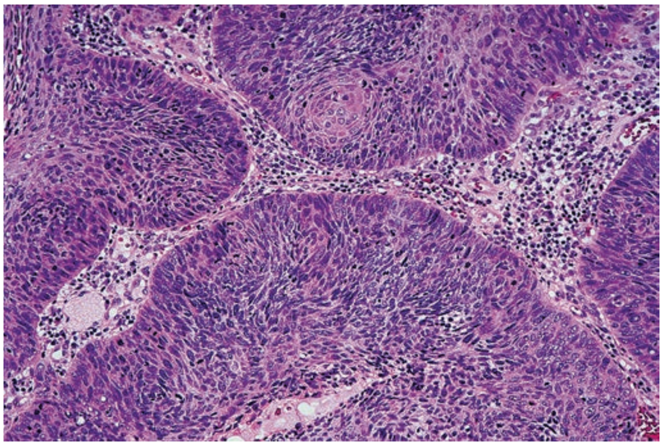

Figure 30.13 Basaloid-pattern invasive squamous cell carcinoma of vulva, a pattern typical of HPV-associated vulvar squamous cell carcinoma. Note the peripheral palisading and deep basophilic staining pattern.

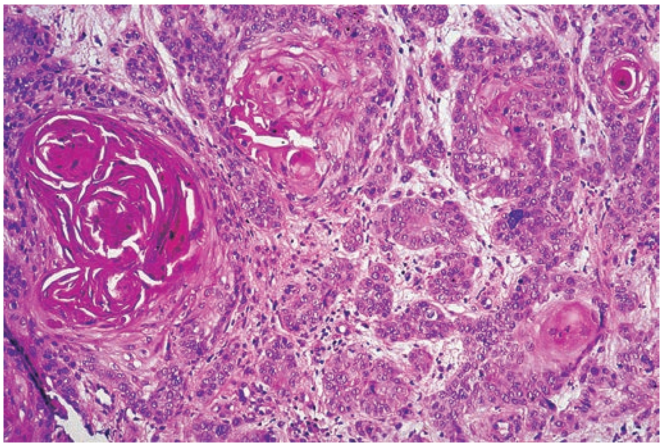

Figure 30.14 Microscopic appearance of invasive well-differentiated keratinizing squamous cell carcinoma of vulva. Such tumors are typically HPV-independent.

Human Papilloma Virus-Independent Invasive Squamous Cell Carcinoma

HPV-independent vulvar squamous cell carcinoma occurs in older women and often is in the setting of lichen sclerosus. Most HPV-independent squamous cell carcinomas are well or moderately differentiated keratinizing squamous cell carcinomas (Fig. 30.14). dVIN may be present at the edge of the lesion, a finding that supports the interpretation that you are dealing with an HPV-independent squamous cell carcinoma. HPV-independent squamous cell carcinoma may be high-grade and, rarely, sarcomatoid, either at presentation or with progression from a more differentiated carcinoma, in the course of recurrence(s). Verrucous carcinoma is a distinctive variant of HPV-independent carcinoma, and will be discussed in a later section.

Spread and Metastases

Regional lymph node metastases occur in approximately 20% of cases.[102] Tumors of the labia spread first to inguinal lymph nodes, whereas those located in the clitoris may metastasize directly into the deep nodes. It should be noted that ulceration and inflammation in vulvar carcinoma often lead to reactive enlargement of inguinal lymph nodes, which may be confused clinically with metastatic disease, so clinical assessment of nodal status is unreliable.

The technique of sentinel lymph node biopsy is used as a staging criterion and therapeutic guide for vulvar carcinoma,[103] and this procedure is highly accurate in predicting the inguinofemoral lymph node status of those patients.[104] The optimal protocol for handling sentinel nodes upon receipt in the laboratory, and the significance of micrometastases or isolated tumor cells, specifically with respect to sentinel nodes associated with vulvar squamous cell carcinoma, remain to be determined; however, the eighth edition of the American Joint Committee on Cancer's *AJCC Cancer Staging Manual* now includes a pN0(i+) category for isolated tumor cells (Table 30.2).[105]

Therapy

The usual treatment of invasive carcinoma is radical vulvectomy with bilateral radical inguinal lymph node dissection.[106] Iliac lymphadenectomy and pelvic exenteration are reserved for advanced cases.[107] Conversely, early cases can be treated with a more conservative approach in the form of wide local excision;[108] it has been shown that leaving a 1-cm tumor-free surgical margin results in a high rate of local control.[109] Alternative methods include radiation therapy (either alone or together with chemotherapy[110]) and the combination of wide local excision and radiation therapy.[111,112]

Prognosis

The overall 5-year survival rate in patients treated for vulvar squamous cell carcinoma has been in the 50%–75% range in most large series.[112–114]

1. *Stage*. The most important prognostic factors are included in the staging system and are represented by *tumor diameter*, *depth of invasion*, and *lymph node status*.[109,113,114,115–117] The latter is by far the most significant parameter.[118,119]
2. *Extracapsular nodal spread*. In cases with involved nodes, the presence of extracapsular spread and large size of the metastatic focus are poor prognostic indicators.[120,121]
3. *HPV status*. As noted previously, HPV-associated vulvar carcinomas are associated with a more favorable prognosis, as has also been seen for squamous cell carcinomas of the head and neck. Infiltrative margins,[122,123] fibromyxoid stromal response,[124] and abnormal p53 immunostaining[125,126] are all features that are reported to be prognostic indicators, but also are associated with HPV-independent carcinomas, so it is not clear whether their prognostic significance is independent of HPV status.

Superficially Invasive Squamous Cell Carcinoma

The term *superficially invasive squamous cell carcinoma* is a "Histologic Type" designation in the widely used 2016 update to the College of American Pathologists Protocol for Examination of Specimens from Patients with Carcinoma of the Vulva.[127] This refers to those carcinomas in which the depth of penetration is less than 1 mm (see Fig. 30.13). **Depth of invasion in vulvar carcinoma is the measurement in millimeters from the epithelial-stromal junction of the adjacent, most superficial dermal papilla to the deepest point of invasion.** It should be noted, with humility, that there is suboptimal reproducibility in pathologists' assessments of whether there is invasion, and in measuring the depth of invasion; when 11 pathologists reviewed 50 cases, the number considered to show invasive squamous cell carcinoma ranged from 21 to 44, depending

Table 30.2 Definitions of American Joint Committee on Cancer TNM: Vulva

DEFINITION OF PRIMARY TUMOR (T)

T CATEGORY	FIGO STAGE	T CRITERIA
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	1	Tumor confined to the vulva and/or perineum Multifocal lesions should be designated as such. The largest lesion or the lesion with the greatest depth of invasion will be the target lesion identified to address the highest pT stage. Depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.
T1a	IA	Lesions 2 cm or less, confined to the vulva and/or perineum, and with stromal invasion of 1.0 mm or less.
T1b	IB	Lesions >2 cm, or any size with stromal invasions of >1.0 mm, confined to the vulva and/or perineum
T2	II	Tumor of any size with extension to adjacent perineal structures (lower/distal third of the urethra, lower/distal third of the vagina, anal involvement)
T3	IVA	Tumor of any size with extension to any of the following—upper/proximal two-thirds of the urethra, upper/proximal two-thirds of the vagina, bladder mucosa, or rectal mucosa—or fixed to pelvic bone

DEFINITION OF REGIONAL LYMPH NODE (N)

N CATEGORY	FIGO STAGE	N CRITERIA
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no >0.2 mm
N1	III	Regional lymph node metastasis with one or two lymph node metastases each <5 mm, or one lymph node metastasis ≥ 5 mm
N1a[a]	IIIA	One or two lymph node metastases, each <5 mm
N1b	IIIA	One lymph node metastasis = 5 mm
N2		Regional lymph node metastasis with three or more lymph node metastases, each <5 mm, or two or more lymph node metastases = 5 mm, or lymph node(s) with extranodal extension
N2a[a]	IIIB	Three or more lymph node metastases, each <5 mm
N2b	IIIB	Two or more lymph node metastases ≥ 5 mm
N2c	IIIC	Lymph node(s) with extranodal extension
N3	IVA	Fixed or ulcerated regional lymph node metastasis

DEFINITION OF DISTANT METASTASIS (M)

M CATEGORY	FIGO STAGE	M CRITERIA
M0		No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	IVB	Distant metastasis (including pelvic lymph node metastasis)

[a] Includes micrometastasis, N1mi and N2mi.

Note: The site, size, and laterality of lymph node metastases should be recorded.

From Amin MB, Edge S, Greene F, et al. eds.. *AJCC Cancer Staging Manual.* vol. 8. New York: Springer; 2017.

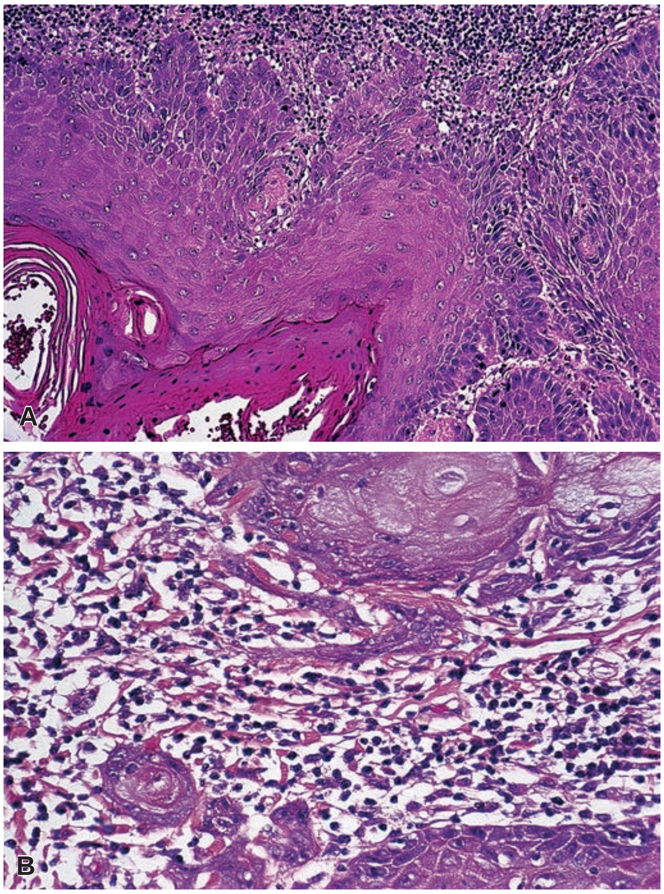

Figure 30.15 **Superficial Invasive Squamous Cell Carcinoma.** **A**, Low-power appearance. **B**, High-power view, showing small clusters of tumor cells detaching from the in situ component and invading a heavily inflamed stroma. All invasive cells are present within 1 mm of the overlying epidermal-dermal junction.

on the reviewing pathologist.[128] This limitation notwithstanding, in those tumors where depth of invasion is considered to be less than 1 mm (Fig. 30.15), consideration can be given to forgoing lymph node sampling, although some oncologists would offer even these patients sentinel lymph node biopsy.

Verrucous carcinoma is a reasonably distinctive type of squamous cell carcinoma of the vulva, similar to its more common counterpart in the upper aerodigestive tract. It may grow to quite large dimensions, has a typical exophytic appearance, and infiltrates locally (Figs. 30.16 and 30.17). Metastases are practically nonexistent,[129,130] and therefore inguinal lymphadenectomy is not indicated.

The differential diagnosis of verrucous carcinoma includes condyloma acuminatum and conventional squamous cell carcinoma. It is distinguished from the former by its generally larger size and the presence of club-shaped fingers of epithelium invading the underlying stroma in a well-circumscribed ("pushing") fashion.[131] The distinction from squamous cell carcinoma rests entirely on two criteria, which often go together: the presence in the latter of cytologic atypia and/or a clearly infiltrative pattern of growth. The occurrence of either of these features removes the lesion from the verrucous carcinoma category and puts it into the squamous cell category. Immunohistochemically, staining for keratin is more uniform and homogeneous in verrucous carcinoma than in squamous cell carcinoma.[132]

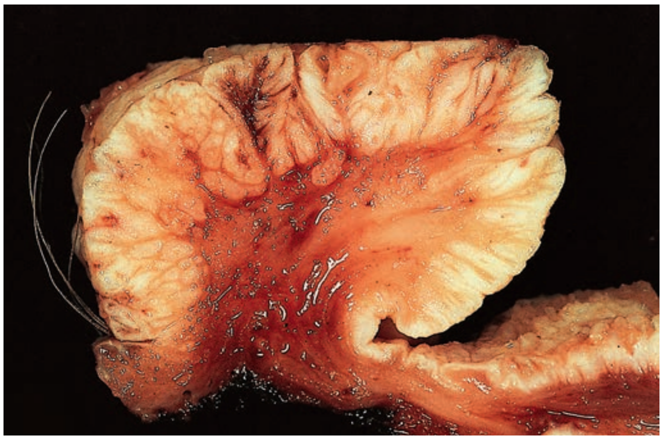

Figure 30.16 Cut surface of verrucous carcinoma of vulva. (Courtesy of Dr Pedro J Grases Galofré; from Grases Galofré PJ. Patología ginecológica. *Bases para el diagnóstico morfológico.* Barcelona: Masson; 2002)

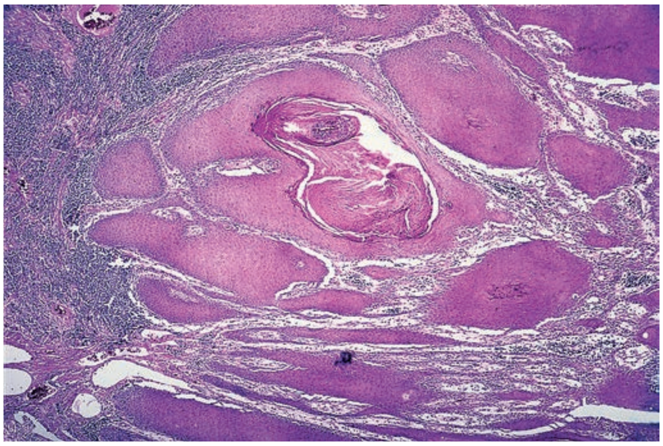

Figure 30.17 Bulbous pegs of well-differentiated squamous cells infiltrate the stroma in vulvar verrucous carcinoma.

Paget Disease

Paget disease is a malignant tumor of the vulva that can be subclassified as primary Paget disease, or secondary Paget disease when it represents spread from an underlying carcinoma of rectum, bladder, or endocervix. The former is far more common in practice, and will be the focus of the following discussion. Paget disease is a vulvar adenocarcinoma of uncertain histogenesis. It could be viewed as a sweat gland carcinoma arising primarily from the intraepidermal portion of the glands (acrosyringium),[133] as a carcinoma of multipotential (adnexal stem cells) residing in the infundibulo-sebaceous unit of the hair follicles and other adnexal structures that differentiate along glandular (sweat gland) lines,[134] or as being derived from a population of CK7-positive clear cells associated with the openings of the ducts of the mammary-like glands of the vulva, known as Toker cells.[135]

Clinically, Paget disease presents as a crusting, elevated scaling erythematous rash in the labia majora, labia minora, and/or perineal skin of adult and elderly patients (Fig. 30.18). Microscopically, the epidermis contains large pale tumor cells that form solid nests, glandular spaces, or a continuous layer along the epidermal basement membrane and also in pilosebaceous structures and sweat ducts

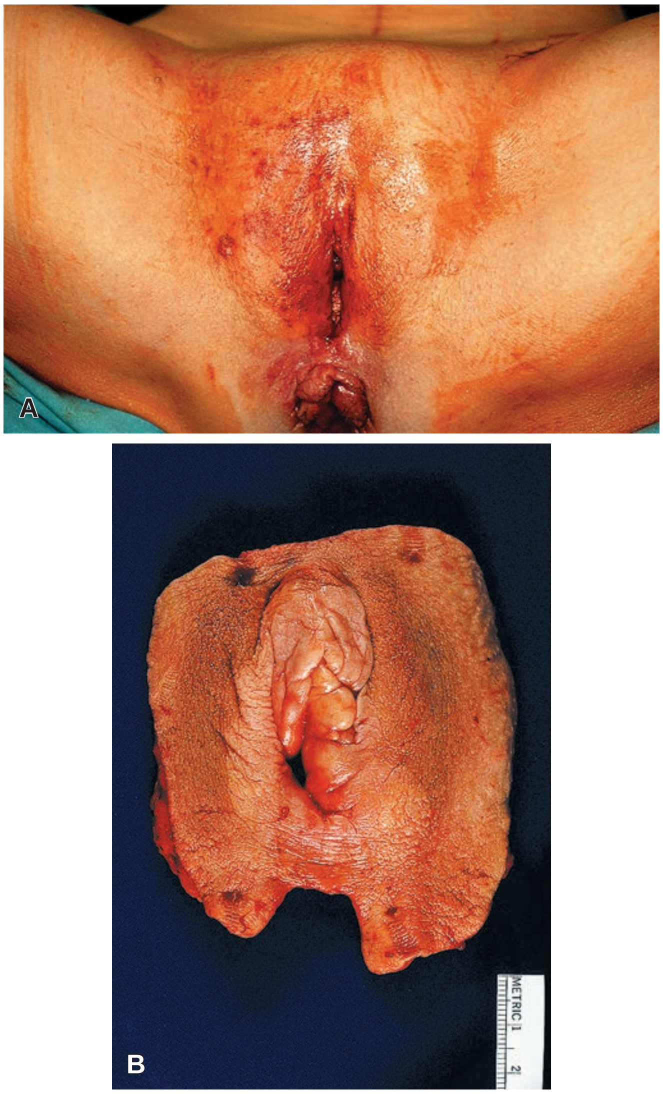

Figure 30.18 **A** and **B**, Clinical and gross appearance of vulvar Paget disease. In both cases the disease is very extensive.

(Fig. 30.19). A cleft often develops between the row of malignant cells and the overlying keratinocytes, resulting in a low-power appearance sometimes reminiscent of an acantholytic suprabasal bulla. Paget disease can also be misinterpreted as malignant melanoma. It should be noted that the presence of melanin granules in some tumor cells *does not* rule out the diagnosis of Paget disease. Histochemically, some or all of the tumor cells contain acidic mucin, as evidenced by their positivity for Mayer mucicarmine and aldehyde fuchsin stains.[136] Immunohistochemically, these mucins are positive for MUC1 and MUC5AC, the latter in striking contrast with Paget disease of the breast.[137,138] They are also reactive for HGM-45, a marker associated with gastric surface mucous cells.[139] Vulvar Paget disease also expresses pankeratin, cytokeratin 7 (CK7), epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), B72.3, and GCDFP-15 (a marker of apocrine differentiation) (Fig. 30.20).[140–144] S-100 protein is positive in up to one-third of the cases, depending on the immunostaining protocol used, and HMB-45 and Melan-A are negative.[145,146] There is also negativity for CDX-2, in contrast to a secondary Paget disease associated with rectal carcinoma.[147] Vulvar Paget disease variably expresses estrogen and progesterone receptors and frequently expresses androgen receptor.[148,149]

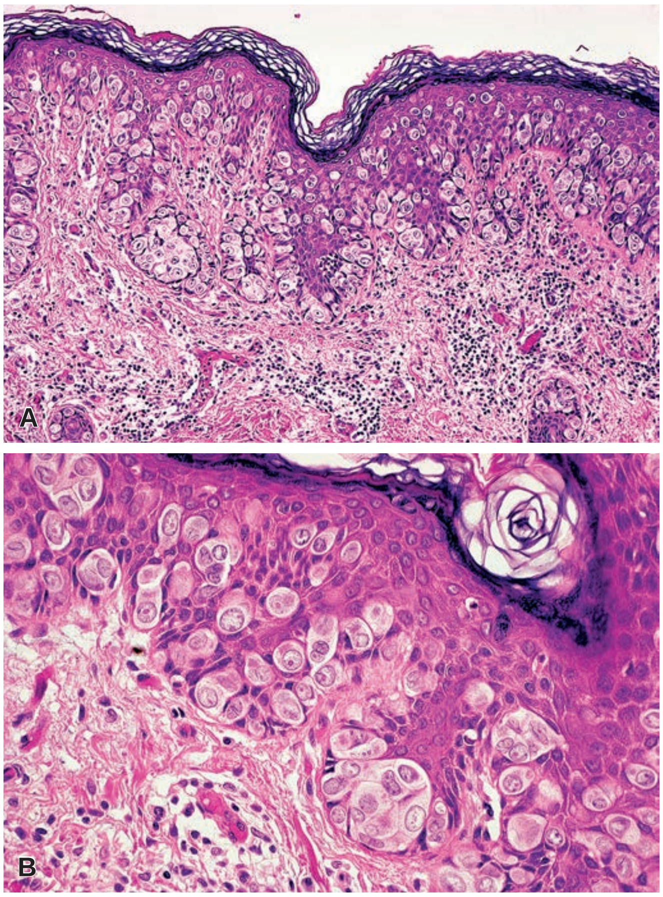

Figure 30.19 **A** and **B**, Low- and medium-power appearances of vulvar Paget disease. The large clear tumor cells are distinct from the malpighian layer.

Regarding the keratins, the usual profile of primary vulvar Paget disease is CK7+/CK20–.[150,151] If it is instead CK20+ (and GCDFP-15 negative), the possibility of secondary Paget disease (especially of rectal or urothelial nature) should be suspected.[150,152] Confirmation of the latter can be obtained with uroplakin-III immunostains.[153] A recent study has reported that nuclear GATA3 expression is typical of primary vulvar Paget disease, a potential diagnostic pitfall when considering secondary urothelial carcinoma.[154] Overexpression and amplification of HER2 is found in a subset of cases.[155]

As already indicated, Paget disease of the vulva differs in several respects from Paget disease of the breast. The latter is nearly always associated with an underlying carcinoma, which may be intraductal or invasive, and the intraepidermal malignant cells are more often than not mucin-negative. In contrast, the majority of the cases (about 90%) of vulvar Paget disease are not associated with an invasive carcinoma[156] and are usually (although not always) positive for mucin stains, as previously noted.[157–159] The incidence of invasive carcinoma ("invasive Paget disease") in primary vulvar Paget disease ranges from 0%–30% depending on the series,[160–162] with some of the invasive cases being in the microinvasive or minimally invasive (>1 mm) category, a finding not associated with lymph node or distant metastases, based on a limited number of reported cases.[163]

If no invasive component is found in the resected specimen, the prognosis is good. Metastases do not occur under these circumstances, although local recurrence is common (about 30%), sometimes in the form of invasive carcinoma.[156,163,164] Therefore, excision should include a margin of normal skin and the underlying subcutaneous

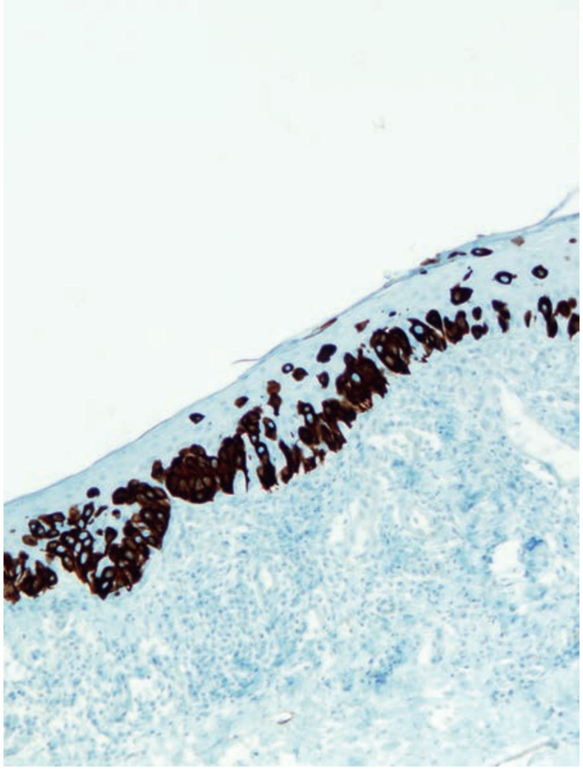

Figure 30.20 Cytokeratin 7 expression in vulvar Paget disease.

tissue. Unfortunately, the microscopic extent of the disease is often greater than that suspected from clinical examination, and this should be taken into account at the time of surgery.[165] The status of resection margins is only minimally related to the incidence of local recurrence.[163] In some instances local recurrence has been seen in the vulvar split-thickness skin graft.[166] Cases of Paget disease with an invasive component beyond the microinvasive stage have a high likelihood of nodal involvement.[163]

Other Epithelial Tumors

Hidradenoma papilliferum is a benign vulvar tumor that usually presents as a small, well-circumscribed nodule covered by normal skin. Occasionally, it ulcerates through the skin and clinically may simulate carcinoma. Microscopically, it has a complex papillary glandular pattern, with stratification and some degree of pleomorphism and mitotic activity, sometimes brisk.[167] A myoepithelial layer is always apparent (Fig. 30.21). Traditionally, this tumor has been regarded as being of sweat gland origin. However, its close morphologic and immunohistochemical similarity to intraductal papilloma of the breast and nipple adenoma suggests an origin from vulvar mammary-like tissue. All acceptable examples of this tumor have behaved in a benign fashion.[168,169] However, a case of intraductal carcinoma of mammary-type apocrine epithelium has been reported as arising from this tumor.[170]

Benign lesions of epidermal or skin adnexal type occur in the vulva. These include *verruca vulgaris*,[72] *syringoma*,[171] *chondroid syringoma* (benign mixed tumor),[172] *myoepithelioma*,[173] *pigmented apocrine hamartoma*,[174] *adenolipoma*,[175] *benign pilar tumor*,[176] *other trichogenic tumors*,[177] *warty dyskeratoma*,[178] and *inverted follicular keratosis*.[179] Although not necessarily a benign skin adnexal tumor, we thought of mentioning here also the occasional occurrence of vulvar *keratoacanthoma*.[180,181]

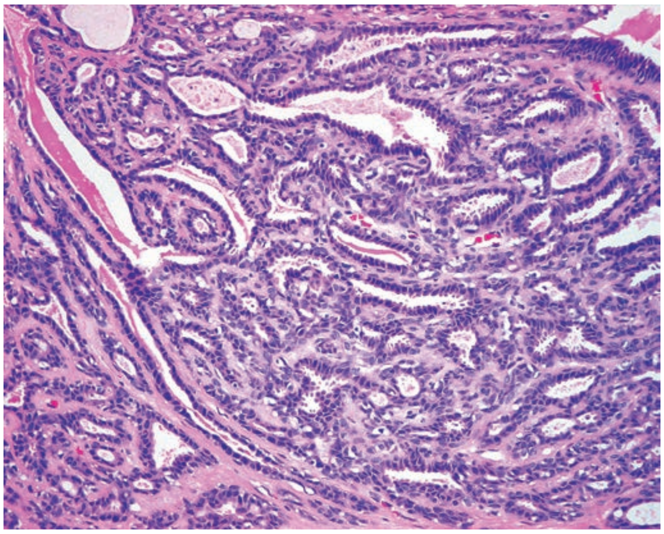

Figure 30.21 Hidradenoma papilliferum of vulva. This tumor probably arises from ectopic breast tissue.

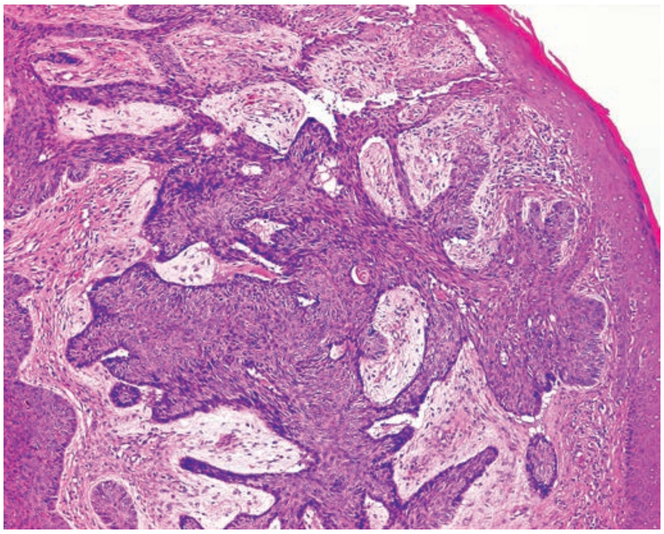

Figure 30.22 Basal cell carcinoma of vulva. It is important to distinguish this tumor from squamous cell carcinoma, especially the basaloid variant of the latter.

Basal cell carcinoma of the vulva usually presents as a nodular mass in the labia majora of elderly patients; it may grow very large and ulcerate.[182,183] Its microscopic appearance and behavior are the same as those of basal cell carcinomas elsewhere in the skin, and solid, keratotic, and adenoid types have been described (Fig. 30.22). The differential diagnosis includes HPV-associated squamous cell carcinoma with a basaloid pattern.[101] It should be remembered that, as elsewhere in the skin, basal cell carcinoma may exhibit abrupt squamous differentiation of possible follicular type, a change that does not affect the natural history of the lesion; such tumors should not be referred to as basosquamous carcinomas.

The incidence of nodal metastases in vulvar basal cell carcinoma is extremely low and is largely restricted to deeply invasive lesions.[183]

Merkel cell carcinoma has been reported in the vulva, sometimes in association with HPV-associated squamous neoplasia (invasive or intraepithelial).[184,185] Its behavior has been very aggressive.[186]

In a single case tested, there was no evidence of Merkel cell polyomavirus.[185]

Sweat gland carcinoma of the vulva is exceptional; it may present with a variety of morphologic patterns and should be distinguished from metastatic adenocarcinoma.[187] A case has been described showing *mucinous and neuroendocrine* features,[188] another with features of *malignant myoepithelioma*,[189] and another resembling *polymorphous low-grade adenocarcinoma* of the salivary glands[190] (see also under Bartholin gland).

Sebaceous carcinoma can occur in the vulva; its appearance is similar to that of its more common counterpart in the head and neck region.[191]

Melanocytic Tumors

Melanocytic nevi occur in the vulva, particularly in the labia majora. Those seen in adults are nearly always of intradermal or compound type. Sometimes, a prominent junctional component is seen in nevi of younger women, in which the enlarged junctional nests vary in size, shape, and position, and may lead to an overdiagnosis of malignant melanoma.[192,193] The term (*atypical*) *genital nevus* is sometimes employed for this microscopically troublesome lesion, which may exhibit a striking degree of cytologic and architectural atypia.[194,195] Benign lentigo (lentigo simplex) may also occur on the vulva. Genital melanotic macules are typically larger (up to 1.5 cm) than a lentigo; while they show similar basal hyperpigmentation to lentigo, there is typically less epidermal hyperplasia. There may be dermal melanophages present.

Melanoma is the second most common malignant tumor of the vulva, following squamous cell carcinoma and representing roughly 5% of all malignant tumors at this site.[196,197] The large majority of the patients are older than 50 years at the time of diagnosis, a fact of great importance in the differential diagnosis with genital nevus.[198,199] Most lesions are advanced (Clark level III or IV) at the time of diagnosis (Fig. 30.23).[200] The microscopic appearance is similar to that of cutaneous melanoma (see Chapter 3) (Fig. 30.24A). An important differential diagnosis is with Paget disease, a situation complicated by the fact that on occasion the two tumors coexist.[201] Sometimes the melanoma is formed of spindle cells growing in fascicles and simulating sarcoma (see Fig. 30.24B).

The usual treatment is radical vulvectomy with bilateral inguinal lymph node dissection, but small lesions with depths of ≤1.75 mm may be treated with wide local excision.[202–204] The overall 5-year survival rate is approximately 35%.[205,206] Lymph node status, level or thickness of the primary tumor, and ulceration are the most important prognostic parameters.[206–210] There is some suggestion that the DNA ploidy pattern may also provide prognostic information.[211] Vulvar melanomas may have c-KIT or NRAS mutations more frequently than melanomas arising at other anatomic sites, but BRAF mutations are rare.[212–214]

Malignant blue nevus of the vulva leading to ovarian metastases has been recorded.[215]

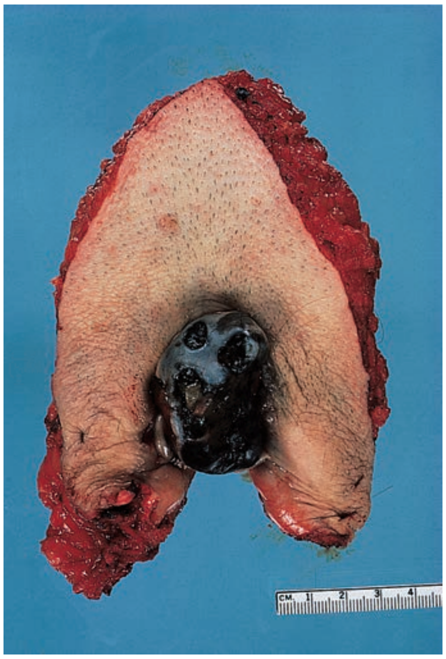

Figure 30.23 Gross appearance of vulvar malignant melanoma. The tumor is large, polypoid, deeply pigmented, and ulcerated.

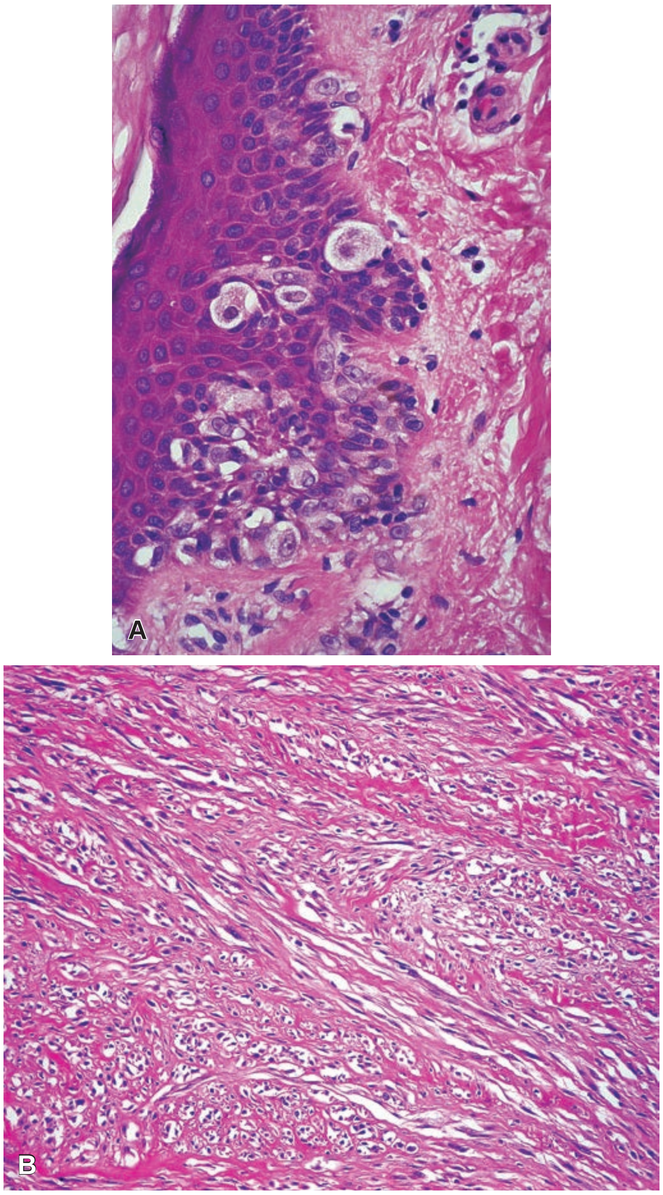

Figure 30.24 Malignant Melanoma of Vulva. A, Superficially spreading type, showing typical intraepidermal growth of pagetoid cells. **B**, Melanoma growing in the form of fascicles of spindle cells and simulating a mesenchymal neoplasm.

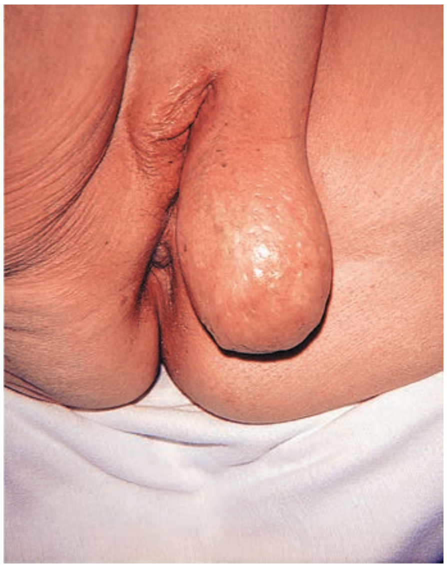

Figure 30.25 Aggressive angiomyxoma protruding in a polypoid fashion through one of the labia.

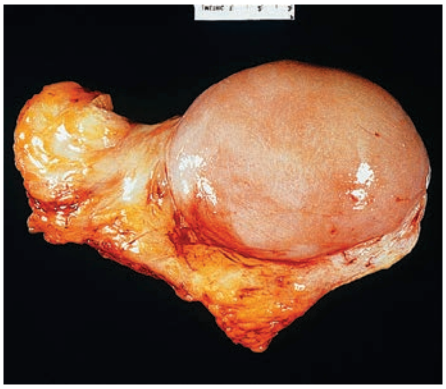

Figure 30.26 Cut surface of vulvar aggressive angiomyxoma. The tumor is soft, gelatinous, and appears encapsulated.

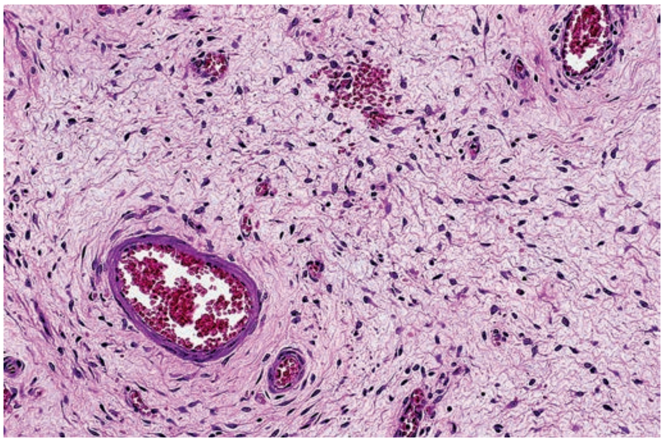

Figure 30.27 Microscopic appearance of aggressive angiomyxoma. The lesion is hypocellular and features large-sized vessels.

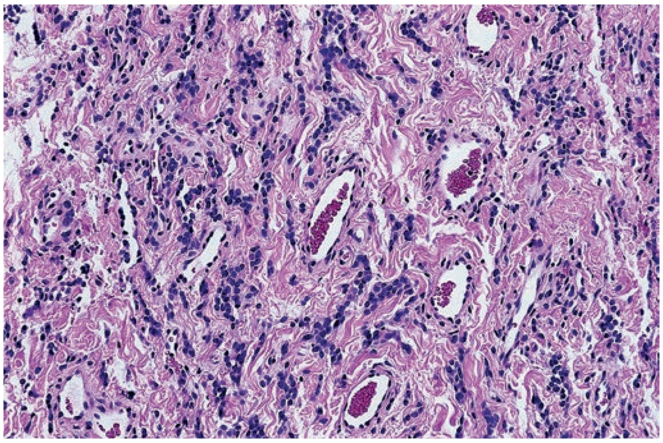

Figure 30.28 Vulvar angiomyofibroblastoma. Rows of small oval cells are separated by fibrous strands.

Aggressive Angiomyxoma and Related Lesions

Aggressive angiomyxoma is a soft tissue neoplasm that usually arises within the perineum. It often presents as a vulvar mass and clinically simulates a Bartholin gland cyst (Fig. 30.25).[216,217] Most patients are in the second or third decade of life, but cases have also been reported in children.[217,218] A similar tumor has been described in the scrotal region in males.[219]

Grossly, the appearance is edematous and ill-defined (Fig. 30.26). Microscopically, a hypocellular stroma devoid of atypicality or mitotic activity is seen intermingling with sizable vessels having dilated lumina and frequent hyaline thickening of the adventitia (Fig. 30.27). This tumor is distinguished from the more common and innocuous fibroepithelial polyp described below because of its larger size, deeper location, and lack of bizarre stromal cells. The differential diagnosis also includes angiomyofibroblastoma, cellular angiofibroma, and massive vulvar edema (see later). Superficial angiomyxoma is a closely related tumor that, as its name implies, has a more superficial location (frequently exophytic) and also differs from aggressive angiomyxoma in being well circumscribed.[220] The ultrastructural and immunohistochemical features of aggressive angiomyxoma are those of primitive mesenchymal cells focally exhibiting myoid traits.[221,222] Stains for acidic mucins are only weakly positive, suggesting that the stroma is more edematous than myxoid. Immunohistochemically, there is positivity for desmin (less so in the male counterpart of this lesion), smooth muscle actin (about half of the cases), CD34 (about half), and estrogen and progesterone receptors (100%, irrespective of gender).[223,224] One-fourth of the cases also show keratin AE1/AE3 positivity.[225] Some cases analyzed cytogenetically have shown a chromosomal translocation involving the region 12q14–15,[226] where the high mobility group AT-hook 2 gene *HMGA2* is translocated, resulting in overexpression of this molecule.[227–229] It should be noted that HMGA2 overexpression is not specific for aggressive angiomyxoma and can be seen in other neoplasms, including leiomyoma.[229] One case of aggressive angiomyxoma was found to have a t(5;8)(p15;q22) translocation.[230]

Recurrence in the ischiorectal and retroperitoneal spaces is common, probably because of the difficulties encountered in achieving a complete surgical excision.[231] In addition, two typical cases have been reported in association with lung metastases.[232,233] Dramatic response to therapy targeting the hormone receptors on the tumor cells has been reported.[234]

Angiomyofibroblastoma is a benign vulvar tumor characterized by alternating hypercellular and hypocellular areas admixed with small blood vessels.[235–237] Spindle and plump stromal cells aggregate around the vessels (Fig. 30.28). These cells are immunoreactive for

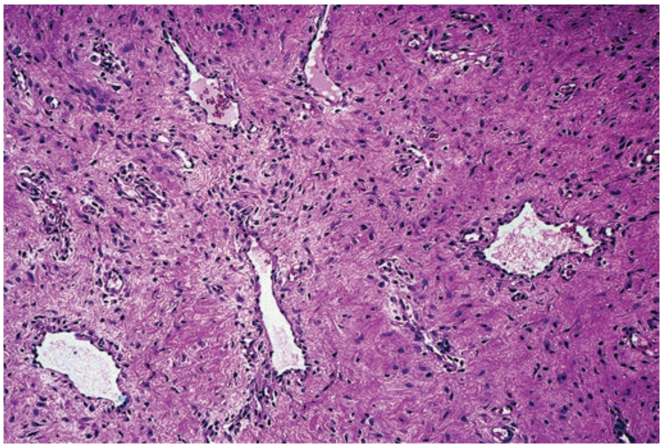

Figure 30.29 Angiofibroma of vulva. The microscopic appearance is reminiscent of nasopharyngeal angiofibroma. (Slide courtesy of Dr. Robert E Scully, Boston, MA)

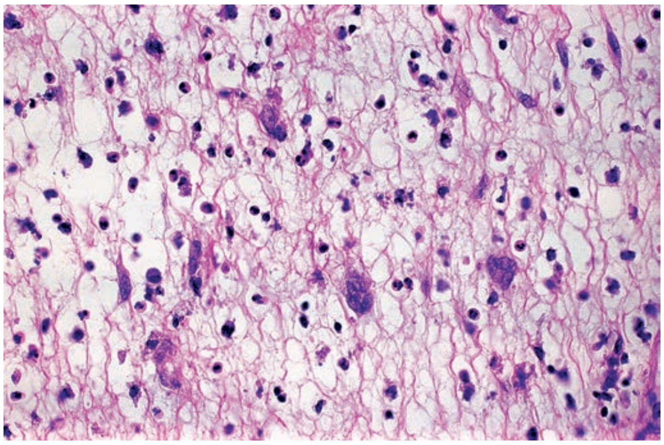

Figure 30.30 Vulvar polyp containing reactive stromal cells, some of which are multinucleated.

vimentin, desmin, and hormone receptors, but usually not for actin or keratin.[238,239] There may be a component of mature adipose tissue; when abundant, the tumor is referred to as the *lipomatous variant*.[240] The behavior is benign, with an extremely low rate of local recurrence, but a case with sarcomatous transformation ("angiomyofibrosarcoma") has been reported.[241] A relationship between angiomyofibroblastoma and tamoxifen therapy has been suggested.[242]

The typical example of angiomyofibroblastoma differs from aggressive angiomyxoma by virtue of its circumscribed borders, higher cellularity, abundance of blood vessels, plump stromal cells, minimal stromal mucin, and rarity of red blood cell extravasation.[235,243] However, enough common features and transitions occur between it and aggressive angiomyxoma to suggest that they are closely related entities.[222,244–246]

Cellular angiofibroma has well-circumscribed margins, like angiomyofibroblastoma. Microscopically, it is composed of uniform, bland, spindle-shaped mesenchymal cells accompanied by numerous thick-walled vessels and inconspicuous islands of mature fat (Fig. 30.29).[247] The tumor is cellular and can be mitotically active.[248] Once again, it is hard to escape the suspicion that this tumor is histogenetically related to the others described in this section, their common denominator being an origin from the specialized hormone receptor–positive mesenchymal tissue within the lower female genital tract.[99,223]

Other Tumors and Tumorlike Conditions

Asymmetric labium majus enlargement in the pre- and early pubertal age may clinically mimic a neoplasm.[249] It tends to regress spontaneously and probably represents an asymmetric physiologic enlargement in response to the normal hormonal surges in this age group.

Massive vulvar edema may be seen secondary to obesity and immobilization.[250] It is similar if not identical to the condition described as *vulvar hypertrophy with lymphedema (or massive localized lymphedema)*.[251] It can simulate aggressive angiomyxoma, but the clinical features should alert the gynecologist and the pathologist to the correct diagnosis.

Fibroepithelial polyp is a superficially located lesion composed of a loose myxoid stroma covered by normal squamous epithelium. Bizarre, stellate, frequently multinucleated cells may be present (Fig. 30.30).[252–254] Some lesions are moderately hypercellular. The combination of hypercellularity and bizarre tumor cells may result in overdiagnosis.[255] As in other sites where this lesion occurs, desmin immunoreactivity may be present.[256]

Prepubertal vulvar fibroma is a controversial entity and some authors regard it as a non-neoplastic hormonally driven lesion identical to **asymmetric labium majus enlargement**.[249,257] It presents at a median age of 8 years. It is grossly ill-defined and is microscopically composed of bland spindle-shaped cells in a variably collagenous to edematous or myxoid stroma lacking atypia and mitotic activity. It may recur locally after excision.[258]

Smooth muscle tumors of both benign and malignant types occur.[259] The leiomyomas include a myxoid variety that can simulate aggressive angiomyxoma,[260] and the leiomyosarcomas include epithelioid and myxoid variants.[261,262] Nielsen et al.[259] evaluated the tumors on the basis of size (≥5 cm), infiltrative margins, mitoses (≥5/10 HPF), and moderate to severe cytologic atypia. Tumors that had three or all four of these features were regarded as leiomyosarcomas, tumors that had none or one of the features were called leiomyomas, and tumors that had two features were designated atypical leiomyomas.

Nonepithelial tumors and tumorlike conditions of many other types have been described in the vulva and its surroundings, most of them of soft tissue type.[263,264] They include *endometriosis, varices*,[265] *hemangioma* and *hemangiomatosis* (sometimes as a component of Maffucci syndrome),[266] *lymphangioma* (which may clinically simulate warts),[267] *angiokeratoma*,[268] *epithelioid hemangioendothelioma*,[269] *glomus tumor*[270,271] and *glomangiomyoma*,[272] *angiosarcoma*[273] (including the *postradiation epithelioid type*),[274] *solitary fibrous tumor*[271] (Fig. 30.31), benign and malignant *granular cell tumors* (some with accompanying pseudoepitheliomatous hyperplasia)[275–277] (Fig. 30.32), *schwannoma*,[278] *neurofibroma(tosis)*,[279,280] *malignant peripheral nerve sheath tumor*,[281,282] *sclerosing lipogranuloma*,[283] *yolk sac tumor*,[284] *rhabdomyosarcoma*[285,286] (usually occurring in children and belonging to the embryonal/botryoid variety), *benign lymphoid hyperplasia*,[287] *verruciform xanthoma*,[288] *Langerhans cell histiocytosis*,[289–291] *nodular fasciitis*,[292] *postoperative spindle cell nodule*,[293] undifferentiated pleomorphic sarcoma,[294] *dermatofibrosarcoma protuberans*[295–297] (including cases with fibrosarcomatous transformation[298]), *Ewing sarcoma/PNET*,[299] *synovial sarcoma*[300] (including the monophasic type[301]), *fibromatosis/desmoid tumor* (sometimes associated with pregnancy),[302,303] *atypical lipomatous tumor*,[304] a lesion resembling *lipoblastoma*,[305] *malignant lymphoma*,[306,307] *paraganglioma*,[308] *alveolar soft part sarcoma*,[309] and *epithelioid sarcoma*.[310]

Epithelioid sarcoma is of importance because of its relatively high frequency at this site and the fact that it tends to run a more

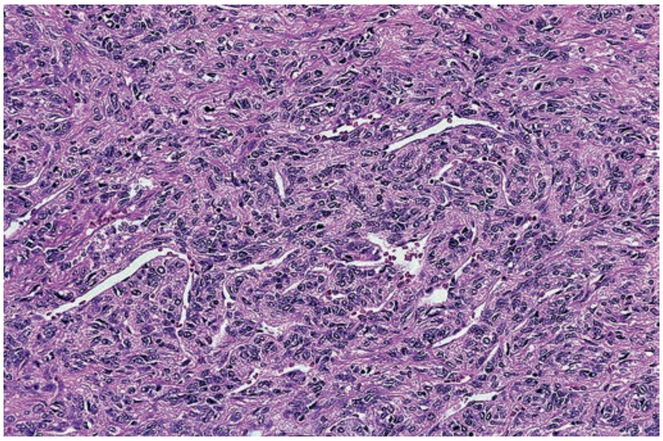

Figure 30.31 A rare example of solitary fibrous tumor involving soft tissues of vulva.

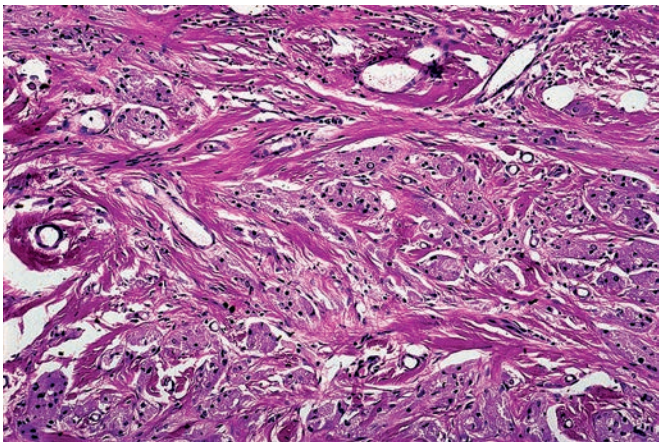

Figure 30.32 Granular cell tumor of vulva.

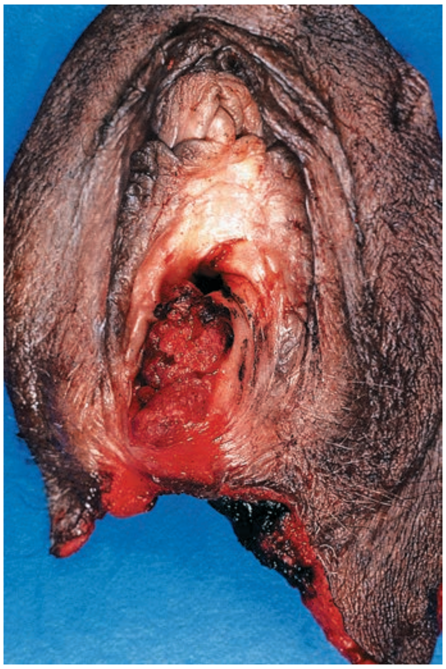

Figure 30.33 Large carcinoma arising from the Bartholin gland.

aggressive course here than in its usual location in the distal extremities. This may at least partially result from the fact that this tumor, when located in the vulva, often exhibits rhabdoid features, known to be associated with an aggressive course.[311] As a matter of fact, it may be difficult to decide whether to designate a vulvar tumor with these features as an epithelioid sarcoma or as a malignant rhabdoid tumor.[312,313] The overlap between these two entities extends to the molecular level as both may show loss of SMARCB1 (INI1) expression.[314] The term proximal-type epithelioid sarcoma has been employed for this particular situation, of which the vulva is a prime example (see Chapter 41).

Metastases to the vulva usually originate from the cervix (almost 50%), endometrium, kidney, or gastrointestinal tract.[315] Most are expressions of generalized disease.[316] The labium majus is the most common location.[317]

Lesions of Bartholin Glands and Related Structures

Cysts and abscesses of the Bartholin glands are the result of chronic bacterial inflammation. The lining of the cyst, which is usually of transitional or squamous type, can be destroyed partially or totally by the inflammatory infiltrate. The nature of the cyst can be established by the presence of residual mucinous glands in the fibrotic and inflamed connective tissue that forms the cyst wall. The secretion product is a nonsulfated sialomucin.[4] Sometimes, extravasation of this mucus into the stroma may induce changes similar to those seen in "mucocele" of the oral cavity.[318] The cyst may be treated by excision or marsupialization.[319] Exceptionally, the inflammatory infiltrate is found to have the features of *malakoplakia*.[320]

Mucous cysts of the *vulvar vestibule* are usually solitary and lined by mucin-producing columnar cells.[321]

Benign tumors and tumorlike conditions of this area include adenoma of minor vestibular glands[322] (which may well represent focal hyperplastic changes secondary to trauma and inflammation), nodular hyperplasia, adenomyoma,[323] mucinous cystadenoma,[324] and papilloma.[325]

Carcinomas of the Bartholin gland[326–329] may take the form of squamous cell carcinoma (the most common) (Fig. 30.33), adenocarcinoma,[330] urothelial (transitional cell) carcinoma, a variant of HPV-associated squamous cell carcinoma (Fig. 30.34), salivary gland–type basal cell and epithelial-myoepithelial adenocarcinoma,[331,332] small cell (neuroendocrine) carcinoma,[333] and adenoid cystic carcinoma (including the tubular variety) (Fig. 30.35).[334–336] Lymph node metastases are common. HPV is often found in the squamous cell carcinoma type,[337] as well as in the transitional cell carcinoma type.[338] The adenoid cystic carcinomas can have the NF1B gene rearrangements, similar to those commonly seen in salivary gland adenoid cystic carcinomas.[339] The overall survival rate is in the neighborhood of 60%.[324,340]

Lesions of the Female Urethra

Urethral caruncle has the appearance of a small raspberry protruding from the meatus; it bleeds easily and may become infected. It occurs only in the female urethra and is not a true neoplasm but rather a reactive polypoid lesion. Microscopically, chronic inflammatory cells, dilated vessels, and hyperplastic epithelium are seen in varying proportions. Mistaken diagnoses of malignancy can result from overinterpretation of islands of reactive epithelium or scattered bizarre stromal or lymphoid cells.[341] There is a tendency for these lesions to recur following excision, probably because of persistence of the original inciting factors.

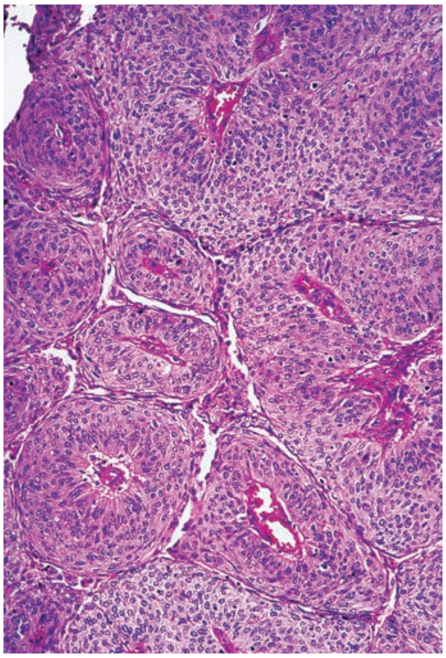

Figure 30.34 Bartholin gland carcinoma of transitional type, a variant of HPV-associated squamous cell carcinoma.

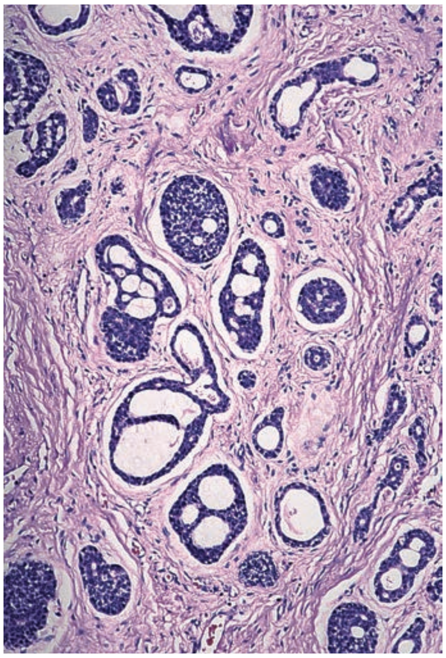

Figure 30.35 Bartholin gland carcinoma of adenoid cystic type.

Prolapse of the urethral mucosa can occur in childhood and clinically simulate a vulvovaginal neoplasm.[342]

So-called **nephrogenic (mesonephric) adenoma** has been traditionally regarded as a metaplastic change resulting from inflammation rather than a true neoplasm. It is microscopically similar to the more common lesions located in the bladder neck.[343,344] Similarly, an occurrence in the urethra of mucinous epithelium of *colonic* type can also be explained on a metaplastic basis, although a congenital origin is also possible.[345]

Villous adenoma has been reported in the urethra in association with tubulovillous adenoma and adenocarcinoma of the rectum.[346]

Urethral carcinoma occurs in elderly patients and presents with bleeding or dysuria.[347,348] The majority of the cases arise from the meatus, at the junction of the transitional and squamous epithelium. In a series of 35 cases, 19 were anterior (vulvourethral), 4 were posterior (vesicoureteral), and 12 involved the entire urethra.[349]

Microscopically, most urethral carcinomas are of squamous cell type.[350,351] Other types include urothelial (transitional cell) carcinoma, columnar/mucinous adenocarcinoma,[352] signet ring adenocarcinoma,[353] and clear cell adenocarcinoma.[354,355] Interestingly, nearly half of the carcinomas reported as arising in urethral diverticula have been adenocarcinomas of either conventional or clear cell type.[356,357] Some of the urethral adenocarcinomas have been associated with adenomatous hyperplasia of the periurethral glands.[358] HPV has been detected by PCR techniques in a high proportion of urethral carcinomas.[359]

The prognosis of urethral carcinoma is relatively poor, except when the disease is limited to the anterior portion of the urethra.[360] In one large series, the 5-, 10-, and 15-year actuarial survival rates were 41%, 31%, and 22%, respectively.[361] The usual treatment is radiation therapy,[361–363] but depending on their size and location, they can also be treated by surgery alone or surgery plus irradiation.[364,365]

Leiomyoma of the urethra, although extremely unusual, is the most common type of benign mesenchymal tumor at this site.[366]

Melanoma of the urethra is a highly aggressive neoplasm that is treated by total urethrectomy with bilateral inguinal lymph node dissection.[367–368]

Malignant lymphoma can exceptionally present as a urethral tumor.[369]

Metastatic tumors in the urethra usually originate in other portions of the female genital tract, particularly endometrium.[351]

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31

Vagina

Blake Gilks

CHAPTER CONTENTS

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Normal Anatomy

The vagina is a tubular structure derived from the paired müllerian ducts that extend from the vestibule of the vulva to the uterus.[1–6] It is composed of three main layers: mucosa, muscularis, and adventitia. The mucosa is composed of stratified squamous epithelium resting on loose connective tissue stroma. The squamous epithelium is responsive to steroid hormones, its appearance depending on the age of the individual and the time of the menstrual cycle.[5]

The subepithelial stroma or lamina propria contains elastic fibers and a rich venous and lymphatic network. Polygonal to stellate stromal cells—some multinucleated—may be present. These cells are immunoreactive for desmin and hormone receptors.

The wolffian (mesonephric) duct in the vagina is represented by *Gartner's duct*,[6] which runs deeply along the lateral vaginal walls. Microscopically, this usually appears in the form of a small single duct, sometimes surrounded by a cluster of small glands, all of them lined by a simple cuboidal epithelium. The presence of inspissated eosinophilic secretion in the lumen is a characteristic feature of these remnants. These cells are immunoreactive for GATA3 and CD10.[7]

Ectopic tissues exceptionally found in the vagina include *prostatic glands*[5] and *sebaceous glands*.[1]

The lymphatic drainage of the vagina is rather complex. The vessels in the upper anterior wall join those of the cervix and terminate in the medial chain of the external iliac nodes (interiliac nodes). Those in the posterior vagina drain into deep pelvic, rectal, and para-aortic nodes. Some of those of the lower vagina (including the hymenal portion) go to the interiliac nodes; others traverse the paravesical spaces and drain into the inferior gluteal nodes. Finally, the vessels that anastomose with those from the vulva drain to the femoral nodes.[2,3]

Adenosis and Related Lesions

Adenosis of the vagina was originally described as a partial or complete conversion of the vaginal mucosa from squamous to endocervical-type glandular epithelium (Fig. 31.1),[8] but the concept was later expanded to embrace the presence of any müllerian-type glandular epithelium in the vagina. Sandberg[9] found occult vaginal adenosis in 9 (41%) of 22 vaginas from postpubertal girls obtained at autopsy but in none of 13 prepubertal patients. Kurman and Scully[10] obtained similar results, suggesting that vaginal adenosis can arise on a congenital basis but that steroid hormones probably play a stimulatory role in their development. Excess mucous discharge is the most common complaint in symptomatic cases. Grossly, adenosis appears as red granular spots or patches that do not stain with Lugol solution. Microscopically, the glands may be mucin-secreting and similar to those of the endocervix (most commonly) or have a lining resembling tubal or endometrial mucosa (Fig. 31.2).[11] Depending on the predominant epithelial component, *mucinous (endocervical)* and *tuboendometrial* forms of vaginal adenosis have been described. The glandular-type epithelium of vaginal adenosis may be in the lamina propria or it may line the surface of the vagina. Chronic inflammation and squamous metaplasia (mature, immature, or atypical) are common accompanying features (Fig. 31.3). The latter, which is poor in cytoplasmic glycogen, can obliterate the glandular lumen and appear as a peg continuous with the surface, a feature that may be misinterpreted as high-grade squamous intraepithelial lesion (HSIL)/vaginal intraepithelial neoplasia 2/3 (VaIN2/3) or even as invasive squamous cell carcinoma.[12] One should be aware, however, that lesions with the features of HSIL (VaIN2/3) can superimpose themselves on foci of adenosis; the identifying features are the same as those described for similar lesions in the chapter on the uterine cervix.

Abstract

The vagina is the least likely part of the female reproductive tract to be sampled for diagnostic purposes, and most pathologic conditions involving the vagina are more commonly encountered in the vulva or cervix. There are exceptions, however, ranging from congenital abnormalities like transverse vaginal septum through to vaginal adenosis, mixed tumor of vagina, and prolapsed fallopian tube at the vaginal apex occurring after hysterectomy. Most neoplasms of the vagina are squamous intraepithelial neoplasia/invasive squamous cell carcinoma secondary to oncogenic HPV. The vagina can also be secondarily involved by tumors arising elsewhere in the reproductive tract, or from extragenital sites.

Keywords

Vagina,
VaIN,
Squamous cell carcinoma,
Fibroepithelial polyp,
Rhabdomyosarcoma,
Mixed tumor

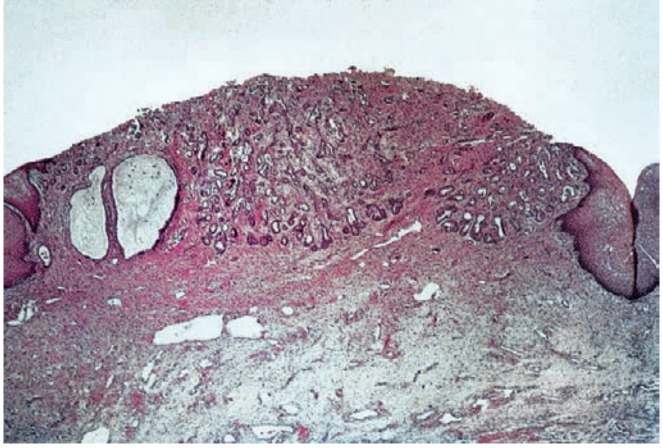

Figure 31.1 Vaginal adenosis with the surface squamous epithelium replaced by glandular epithelium and glands extending down into the superficial lamina propria.

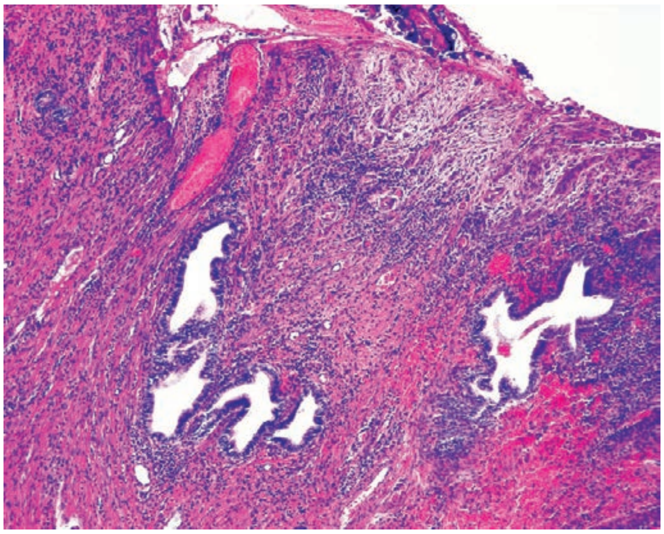

Figure 31.2 Vaginal adenosis of tuboendometrial type beneath an ulcerated surface. Other areas of this specimen showed adenocarcinoma arising from the adenosis.

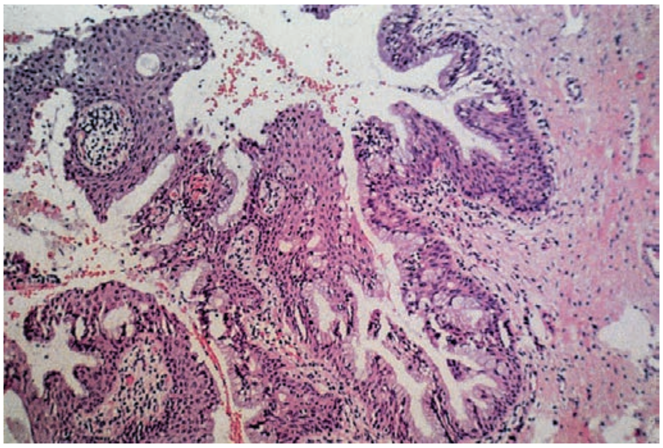

Figure 31.3 Extensive squamous metaplasia in vaginal adenosis.

Sometimes the squamous metaplasia is so extensive that the only evidence of a preexisting adenosis is found in the form of rare intercellular pools or intracellular droplets of mucin, as shown by mucicarmine or other mucin stains. It has been suggested that, as these women grow older, vaginal adenosis regresses by the process of squamous metaplasia.[13]

Microglandular hyperplasia can develop within lesions of vaginal adenosis. It is important not to confuse this benign lesion with adenocarcinoma.[14]

A footnote of historical interest relates to the causal relationship between vaginal adenosis and exposure in utero to diethylstilbestrol (DES). The reported incidence of adenosis in the exposed population has varied from 35% to more than 90% in the different series.[15] It has been shown that the incidence of vaginal adenosis and related colposcopic abnormalities is close to 100% if the drug was begun during or before the eighth week of pregnancy and only 6% if it was begun during the fifteenth week or later.[16] The microscopic features of adenosis in women exposed in utero to DES are identical to those seen in unexposed women.[17,18] **Transverse ridges** and other structural anomalies are also related to DES administration.[19,20] They are found in the upper vagina or cervix in about one-fourth of the exposed population, and microscopically the ridge is composed of a core of fibrous tissue lined by mucinous epithelium, metaplastic squamous epithelium, or, rarely, tubal or endometrial epithelium.

Other Non-Neoplastic Lesions

Transverse vaginal septum is a congenital malformation that occurs as a result of failure of fusion of the distal müllerian duct and the anogenital sinus. It can completely obstruct the vagina and present with primary amenorrhea. Histologically it is characterized by central smooth muscle (not seen in the hymen) and may show adenosis of the epithelium on the proximal side of the septum. It is distinct from the longitudinal vaginal septum associated with duplication (complete or partial) of the genital tract, and it may be associated with other anomalies.[21]

Condylomas can occur in the vagina and show similar papillomatous architecture and viral cytopathic effect (koilocytic change, with large nuclei showing irregular nuclear contours) as condyloma occurring at other body sites, for example, vulva or penis. Indolent infections caused by *Trichomonas vaginalis* and *Candida albicans* are relatively common, especially during pregnancy.[22] **Lymphogranuloma venereum** can involve the vagina during the late stage of the disease and result in stricture. **Xanthogranulomatous reactions**[23] and **malakoplakia**[24] may occur as a result of unusual bacterial infections and lead to pseudotumor formation or strictures (Fig. 31.4). The use of *tampons*, especially if left in place long term, can result in gross vaginal ulcers, as can pessaries.[25]

Occasionally, following vaginal hysterectomy, the **tubal fimbria** may become entrapped in the healing vaginal apex, a finding that must not be confused with a neoplastic process.[26] The clinical presentation is that of a mass grossly resembling "granulation tissue" at the vaginal apex, usually appearing within 6 months following a hysterectomy.[27] Occasionally, the tubal prolapse is associated with an exuberant stromal response with an angiomyofibroblastic appearance, a feature which adds to the diagnostic difficulty.[28]

Endometriosis and the related condition known as **endocervicosis** occur in the vagina, but less commonly than in other genital tract sites.[29] Most cases are seen in connection with episiotomy scars.

Cysts of the vagina can be of several different types.[30] The most common is the *epithelial inclusion cyst*, lined by squamous epithelium and sometimes resulting from surgery or trauma. Another common type is characterized by a simple lining of mucin-secreting, tall columnar, nonciliated epithelium of endocervical type, sometimes

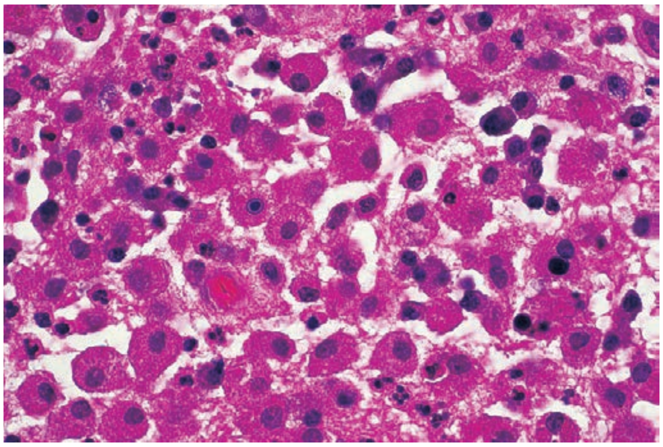

Figure 31.4 **Malakoplakia of Vagina.** This periodic acid–Schiff stain shows numerous histiocytes containing particulate material in their cytoplasm.

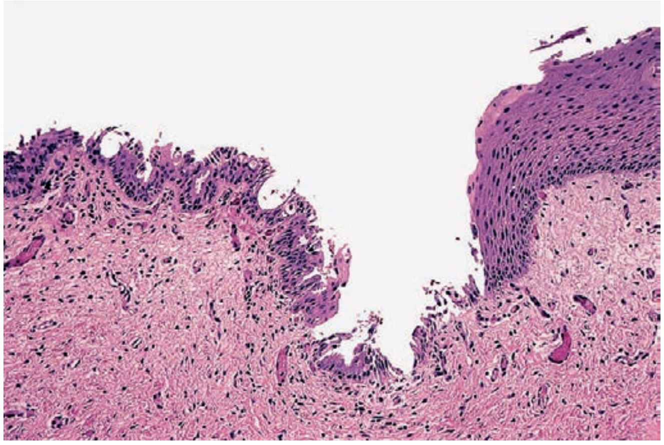

Figure 31.5 Vaginal cyst lined by müllerian epithelium connecting with surface squamous epithelium.

associated with focal squamous metaplasia; this has been designated *müllerian cyst* and can be found anywhere in the vagina (Fig. 31.5). *Mesonephric (Gartner duct) cyst* is rare; it is located in the anterolateral or lateral vaginal wall and is lined by low cuboidal epithelial cells, sometimes ciliated, that do not secrete mucin. Other rare cystic lesions of the vagina include *urothelial cysts* (located in the suburethral portion and probably arising from paraurethral glands and Skene ducts), *emphysematous vaginitis*,[30,31] and the already mentioned *endometriosis*.

Benign Epithelial Tumors

Müllerian papilloma, having a branching configuration and a lining of a single layer of cuboidal cells, has been rarely described in children. It may present on the mucosal surface as polyps or intramurally. *Papillary müllerian cystadenofibroma* of the vagina is probably a histogenetically closely related tumor.[32]

Squamous papilloma may be seen in the adult vagina as a solitary lesion or as multiple small projections (micropapillomatosis). Both variants are unrelated to HPV in most cases.

Tubulovillous adenoma and villous adenoma of the vagina, morphologically similar but immunohistochemically distinct (i.e., positive for ER and CK7 expression) to their colorectal counterparts, have been described.[33,34] They are unrelated to HPV, and their histogenesis is poorly understood at this time but may represent the vaginal counterpart to the HPV-independent adenocarcinoma in situ of the cervix, given that association with invasive adenocarcinoma has been described.

Mixed tumor (spindle cell epithelioma) is usually located in or near the hymenal ring. It is composed of small stromal-type spindle cells intermixed with mature squamous cells and glands lined by mucinous epithelium (Fig. 31.6).[32,35] Ultrastructural and immunohistochemical studies support an epithelial nature.[36] There may also be immunoreactivity for CD34, ER, PR, h-caldesmon, and CD10.[35,37] The lesion is benign, but it may recur locally if incompletely excised.[36,38]

Tubulosquamous polyp is a recently described distinctive vaginal lesion characterized microscopically by the presence of well-circumscribed expansile nests of epithelial cells embedded in a hypocellular fibrous stroma. The epithelial component is generally of both squamous and glandular type, the former predominating.[39] They may be solid/polypoid or cystic, with the former being more commonly located in the upper vagina and the latter in the lower third. Prostatic-type tissue can sometimes be found within this polyp, and the glandular tissue may stain positively for prostate-specific antigen (PSA).[40]

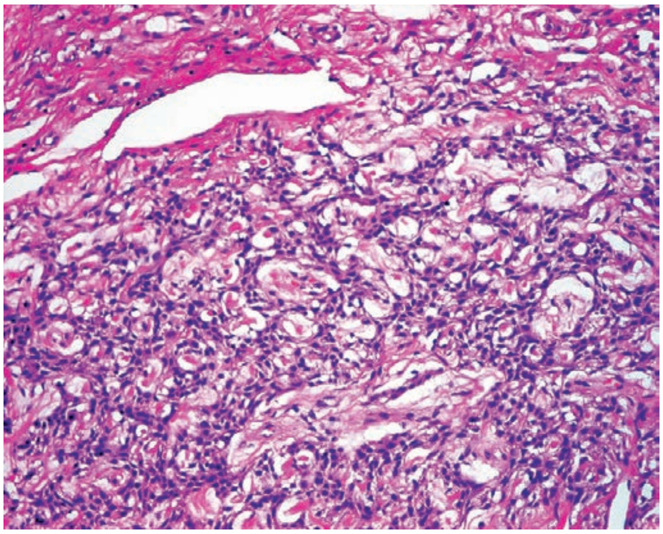

Figure 31.6 **Mixed Tumor of Vagina.** The plexiform pattern of growth seen in this field is characteristic of the entity.

Squamous Intraepithelial Lesions

Atypical premalignant squamous epithelial lesions of the vagina are designated **HSIL (VaIN2/3)**, using the terminology proposed by LAST (Lower Anogenital Squamous Terminology Standardization Project) for squamous intraepithelial neoplasia associated with anogenital HPV infection (Fig. 31.7).[41] It should be noted that the vaginal lesions usually arise from native squamous epithelium, in contrast to most cervical cases, which originate from *metaplastic* squamous epithelium. HSIL (VaIN2/3) is multifocal in about half of cases and very frequently associated with concomitant, subsequent, or prior (in situ or invasive) neoplasms elsewhere in the lower genital tract, especially the cervix.[42–44] The upper third of the vagina is the most common site, in which case the vaginal and cervical lesions may be confluent.[45] The HPV genotype distribution in HSIL (VaIN2/3) is similar to that of HSIL elsewhere in the genital tract.[46] The type of treatment depends largely on the extent of the disease and may

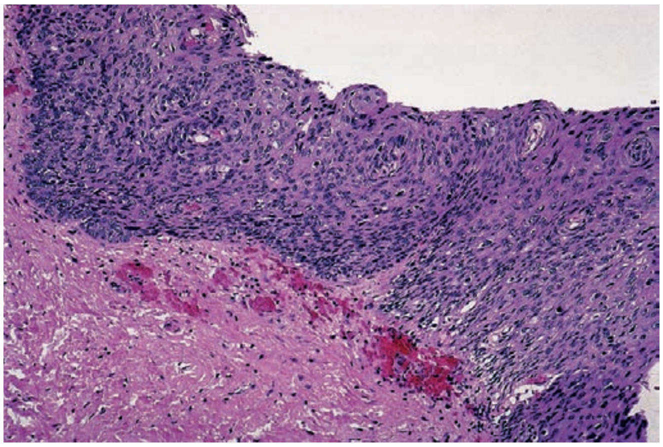

Figure 31.7 High-grade squamous intraepithelial lesions/vaginal intraepithelial neoplasia (HSIL/VaIN3).

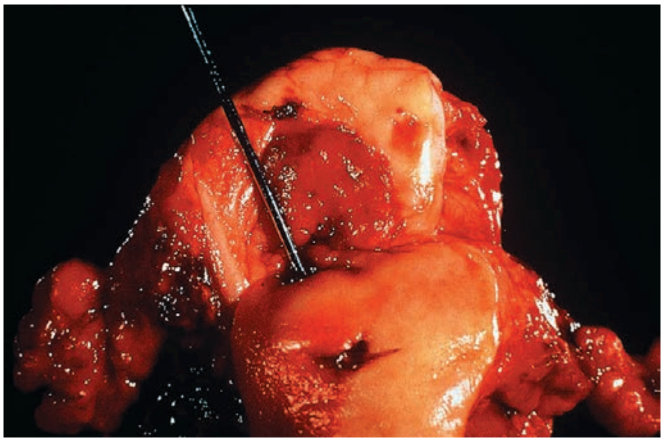

Figure 31.8 Invasive squamous cell carcinoma resulting in a large ulcerated mass.

consist of local excision, partial or total vaginectomy, CO_2 laser therapy, or administration of topical 5-fluorouracil.[42,43,47]

It is important not to overdiagnose transitional cell metaplasia as HSIL (VaIN2/3), the criteria for the differential diagnosis being the same as for the uterine cervix.[48] Additionally, vaginal atrophy may closely mimic squamous intraepithelial neoplasia because of the high nuclear-to-cytoplasmic ratio.

Invasive Squamous Cell Carcinoma

Primary carcinoma of the vagina is much less common than carcinoma of the vulva or cervix and often presents in patients with a prior diagnosis of HSIL or invasive carcinoma of cervix or vulva.[49–51] It is HPV-associated in a large majority of cases and is largely a disease of the elderly.[52,53] As with vulvar squamous cell carcinomas, the HPV-independent tumors are associated with a worse prognosis than the more common HPV-associated squamous cell carcinoma.[54] Since most carcinomas involving the upper vagina represent direct extension from cervical carcinomas, only vaginal tumors that spare the uterine cervix are regarded as primary. Those involving both areas are classified as cervical carcinomas with vaginal extension, regardless of the relative proportion of involvement. The same reasoning holds true for carcinomas involving vulva and distal vagina; these are considered to be vulvar carcinomas with vaginal extension, by convention.

Most primary vaginal carcinomas are grossly nodular or ulcerative (Fig. 31.8).[55] The upper third and the anterior or lateral walls are the most common sites of origin.[56] A few cases have arisen in surgically constructed neovaginas.[57,58]

Microscopically, the morphologic appearance of vaginal squamous cell carcinomas duplicates that of their vulvar counterparts and can be well-differentiated keratinizing type (Fig. 31.9) or can show basaloid or warty morphology (Fig. 31.10).

Vaginal carcinoma is usually treated by a combination of external and intracavitary radiation[59–61]; local excision can be employed for small tumors and radical surgery for selected cases located in the upper vaginal third or posterior wall.[62] The overall 5-year survival rate is between 40% and 50% but is significantly higher (~75%) for patients with stage I disease (Table 31.1).[63] The prognosis is similar whether the patient has a previously treated cervical carcinoma or not.[64] Most recurrences occur within 1 year of therapy and carry an ominous prognosis. Upper lesions tend to recur locally, whereas lower lesions are more commonly associated with pelvic sidewall and distal recurrence.[65]

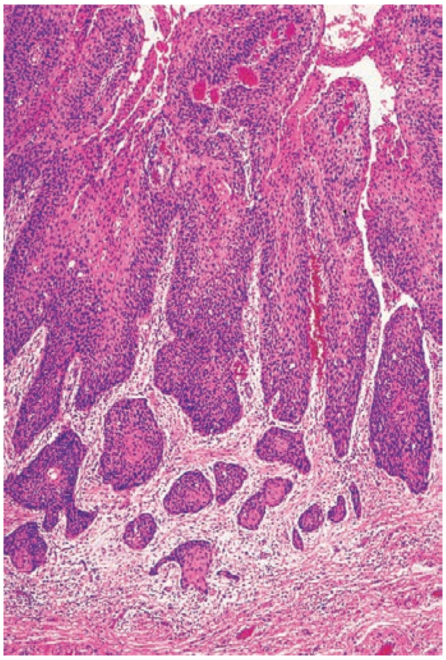

Figure 31.9 Well-differentiated keratinizing squamous cell carcinoma of vagina invading the superficial stroma.

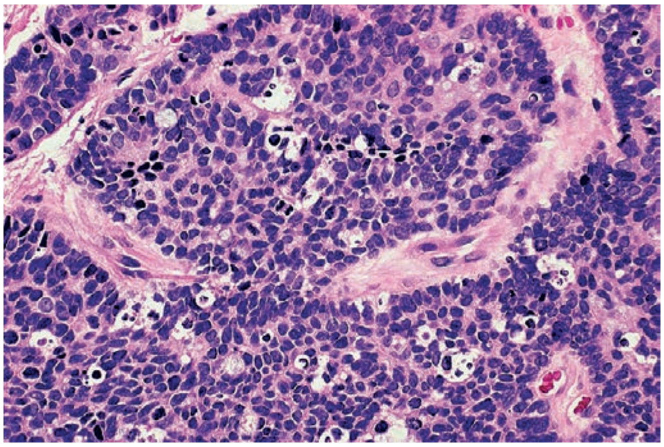

Figure 31.10 Squamous cell carcinoma of the vagina with a more basaloid morphology.

Table 31.1 Definitions of AJCC TNM: vagina

DEFINITION OF PRIMARY TUMOR (T)		
T CATEGORY	**FIGO STAGE**	**T CRITERIA**
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to the vagina
T1a	I	Tumor confined to the vagina, measuring ≤2.0 cm
T1b	I	Tumor confined to the vagina, measuring >2.0 cm
T2	II	Tumor invading paravaginal tissues but not to pelvic sidewall
T2a	II	Tumor invading paravaginal tissues but not to pelvic wall, measuring ≤2.0 cm
T2b	II	Tumor invading paravaginal tissues but not to pelvic wall, measuring >2.0 cm
T3	III	Tumor extending to the pelvic sidewall[a] and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient evidence to classify a tumor as T4)

DEFINITION OF REGIONAL LYMPH NODE (N)		
N CATEGORY	**FIGO STAGE**	**N CRITERIA**
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	III	Pelvic or inguinal lymph node metastasis

DEFINITION OF DISTANT METASTASIS (M)		
M CATEGORY	**FIGO STAGE**	**M CRITERIA**
M0		No distant metastasis
M1	IVB	Distant metastasis

[a] *Pelvic sidewall* is defined as the muscle, fascia, neurovascular structures, or skeletal portions of the bony pelvis. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall.

From Amin M, Edge S, Greene F, et al., eds. *AJCC Cancer Staging Manual*. Vol 8. New York, NY: Springer; 2017.

The existence of *microinvasive (superficially or minimally invasive) carcinoma* as a distinct clinical entity in the vagina has been proposed, but the concept faces the same theoretic and practical difficulties for a precise definition as in the vulva and cervix, a problem exacerbated by the rarity of vaginal carcinoma.[66] The College of American Pathologists checklist for vaginal tumors does include a category of superficial invasive squamous cell carcinoma, defined as 3 mm or less invasion with no lymphovascular invasion, which identifies a group of patients with reduced (but not negligible) chance of lymph node metastases.[66]

Clear Cell Carcinoma

Clear cell (adeno)carcinoma characteristically occurs in the anterior or lateral wall of the upper vagina or in the uterine cervix. Formerly it was most often encountered in children, adolescents, and young adults post in utero exposure to DES.[12,56] Since DES stopped being used during pregnancy, it has become a very rare form of vaginal carcinoma. Microscopically, there are tubules and cysts lined by clear cells alternating with more solid areas and papillary formations (Fig. 31.11).[67] Mitotic figures are variable but usually scanty. The tumor cells have abundant clear cytoplasm because of the presence of glycogen. Intracytoplasmic mucin is either absent or scanty. Hobnail-shaped cells are frequently seen protruding into the glandular lumen. The microscopic differential diagnosis needs to be made primarily with microglandular hyperplasia, which can occur in areas of vaginal adenosis, and the Arias-Stella reaction related to pregnancy or progestational agents. Yolk sac tumor is theoretically in the differential diagnosis but occurs almost exclusively in infancy and early childhood (<4 years old). The immunohistochemical profile of these tumors is not well characterized but appears to be similar to that of the more common clear cell carcinomas of endometrium and ovary.[68]

The prognosis is relatively favorable; small, asymptomatic tumors usually are cured by surgery. Tumors that are large, that are close to the resection margins, or that have penetrated more than 3 mm into the wall tend to recur locally.[69]

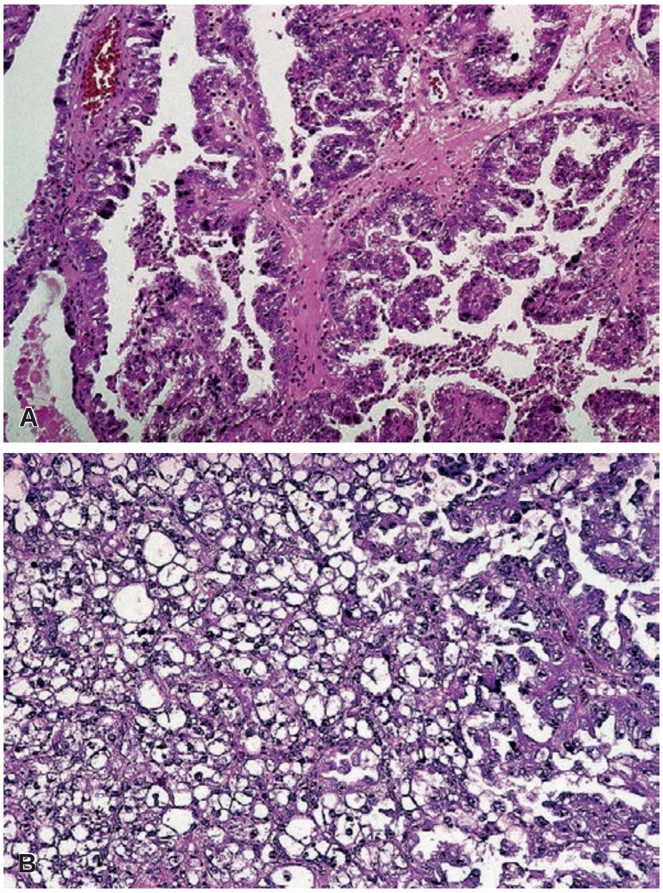

Figure 31.11 **Clear Cell Carcinoma of Vagina. A,** Papillary pattern; **B,** prominent clear cell features.

Other Carcinoma Types

Verrucous carcinoma is an extremely well-differentiated variant of squamous cell carcinoma. Like its vulvar and cervical counterparts, it invades locally but is practically never associated with lymph node metastases. The local spread can be quite extensive and reach the rectum and coccyx.[70] It should be distinguished from condyloma acuminatum, which may rarely involve the vagina; the criteria are the same as those described in the section on the vulva. Most verrucous carcinomas are unrelated to HPV.[71]

Endometrioid adenocarcinoma can occur in the vagina, and most cases are located at the vaginal apex.[72] It is thought to arise on the basis of vaginal endometriosis.[73] The presence of the latter is important in supporting a primary vaginal tumor as opposed to secondary spread from the endometrium. The combination of p16 and ER immunostaining, most commonly used to distinguish HPV-associated cervical adenocarcinoma (diffuse p16 reactivity, ER–) from endometrioid adenocarcinoma of the endometrium (patchy p16 reactivity, ER+) can shed light on the pathogenesis of an adenocarcinoma present in a vaginal biopsy, but cannot distinguish between a primary vaginal adenocarcinoma of endometrioid type arising from endometriosis versus secondary vaginal involvement from an endometrioid carcinoma of endometrium, or primary vaginal adenocarcinoma of HPV-associated type versus secondary involvement by an endocervical adenocarcinoma. Note that metastatic involvement of the vagina is more common than primary vaginal adenocarcinoma, and a primary endometrial or cervical adenocarcinoma must be excluded on clinical grounds as there are no primary site-specific immunomarkers. Endometriosis is also the presumed origin for most cases of adenocarcinoma located in the rectovaginal septum and having no mucosal involvement of either the vagina or rectum.[74,75]

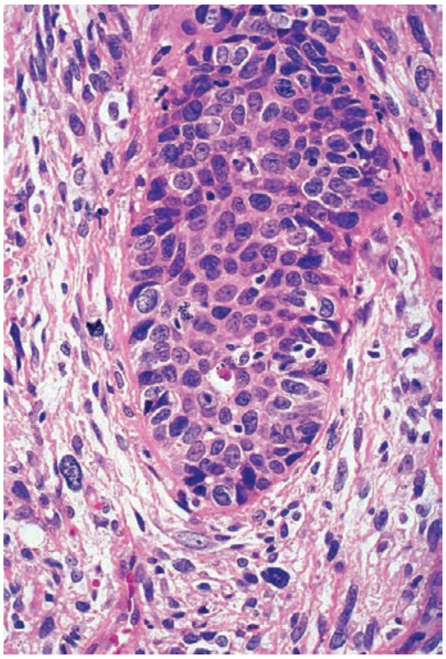

Figure 31.12 Spindle cell (sarcomatoid) carcinoma of vagina. Elongated cells with a mesenchymal-like appearance surround a well-defined nest having a clear-cut epithelial appearance.

Mesonephric (wolffian) adenocarcinoma is an exceptionally rare tumor located paravaginally, along the course of the wolffian-derived ducts of Gartner.[76,77] They morphologically and immunophenotypically resemble the more common mesonephric adenocarcinomas of the cervix and uterine corpus. They may be biphasic, with a spindle cell component.[76]

Sarcomatoid carcinoma (carcinosarcoma) of the vagina is equivalent to the more common sarcomatoid carcinomas of the upper aerodigestive tract (Fig. 31.12).[78,79]

Mucinous adenocarcinoma of vagina has been described in middle-aged and elderly patients, occasionally arising on the basis of endocervicosis.[80] Its microscopic features are indistinguishable from those of its more common endocervical counterpart.[81] In a few reported cases, the appearance has been reminiscent of enteric epithelium.[33,82] Its relationship with HPV is not known at this time.

High-grade (neuroendocrine) carcinoma can occur in the vagina, either in a pure form or associated with squamous or glandular elements.[80,83–85] They can be either small cell or large cell type. Most cases have been treated by a combination of radiation therapy and chemotherapy.[84] A case of neuroendocrine carcinoma of the vagina with a *Merkel cell* phenotype has also been reported.[86]

Other carcinoma types that have been described in the vagina are *urothelial (transitional cell) carcinoma*[87] (including a pagetoid form[88] and a variant described as *papillary squamotransitional*[89]), *lymphoepithelioma-like carcinoma*,[90,91] *basaloid carcinoma*,[92] adenoid basal carcinoma, and adenosquamous carcinoma.

Mesenchymal Tumors and Tumorlike Conditions

Fibroepithelial polyps may be seen in adult women (especially during pregnancy) or in neonates.[93,94] They are probably not true neoplasms but rather manifestations of hormone-induced localized hyperplasia of the loose subepithelial connective tissue zone[95]; others

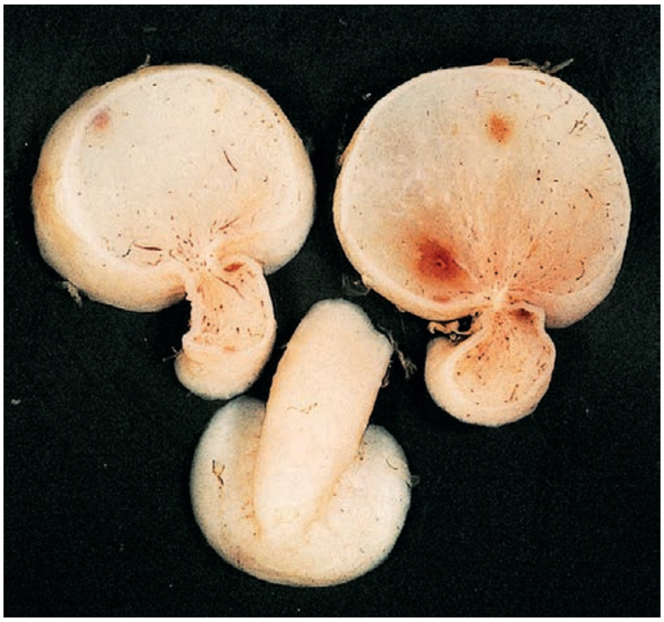

Figure 31.13 Curious mushroom-like appearance of vaginal fibroepithelial polyp. (Courtesy of Dr. Pedro J. Grases Galofré; from Grases Galofré PJ. *Patología ginecológica. Bases para el diagnóstico morfológico*. Barcelona: Masson; 2002.)

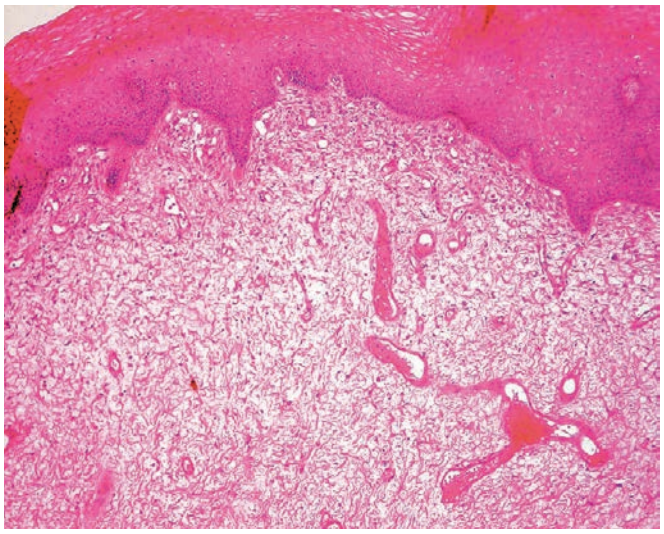

Figure 31.14 Fibroepithelial polyp of vagina showing loose fibrovascular stroma covered by slightly thickened but otherwise unremarkable squamous epithelium.

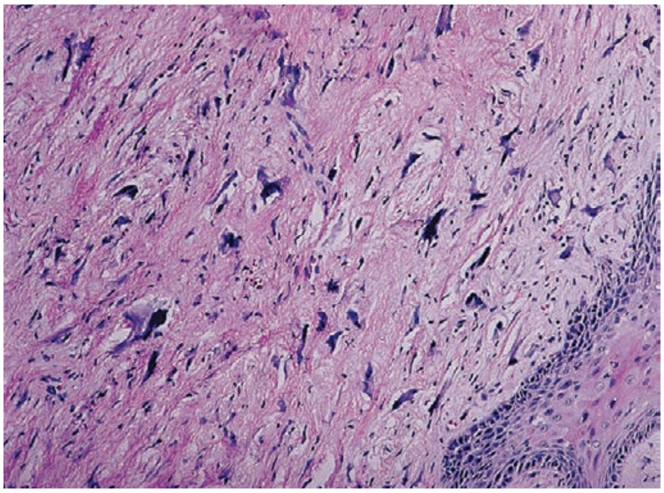

Figure 31.15 Atypical benign stromal cells in a vaginal polyp.

may represent the end stage of granulation tissue (Fig. 31.13).[96] Microscopically, they are formed of a central fibrovascular core and a covering of normal-appearing squamous epithelium (Fig. 31.14). Sometimes the stroma is markedly edematous[95]; in other instances it is hypercellular and/or contains scattered highly atypical stromal cells of stellate shape (Fig. 31.15).[97–100] These stromal cells are commonly immunoreactive for desmin and steroid receptors but usually not for actin.[101,102] The clinical appearance, nuclear atypia, and desmin immunoreactivity may lead to a mistaken diagnosis of embryonal rhabdomyosarcoma or other types of malignant tumor.[94,103] The slow pace of growth at the clinical level and the fact that a cambium layer, epithelial invasion, and cross striations are absent are among the distinguishing features; they also lack expression of the myoblastic markers myogenin and MyoD1 on immunostaining.

Aggressive angiomyxoma can present as a protruding intravaginal mass and extend through the paravaginal soft tissue.[104]

Angiomyofibroblastoma, superficial myofibroblastoma, and **solitary fibrous tumor** are other types of benign mesenchymal neoplasms of fibroblastic/myofibroblastic nature that have been reported in the vagina.[105–107] The angiomyofibroblastoma has an appearance identical to that of its vulvar counterpart, and the superficial myofibroblastoma represents a minor variation on the theme of benign polypoid tumors of the hormonally responsive mesenchymal cells of the region.[108] Solitary fibrous tumor, as in other sites, can be confirmed with *STAT6* nuclear expression by immunohistochemistry.

Postoperative spindle cell nodule is a pseudosarcomatous vaginal lesion that occurs a few weeks following hysterectomy or some other surgical procedure in the region and which presents as a small friable reddish mass in the vaginal vault.[109,110] Microscopically, it shows ulceration, granulation tissue, and a very hypercellular spindle cell proliferation characterized by a fascicular pattern of growth, many mitotic figures, and numerous extravasated red blood cells, resulting in a Kaposi sarcoma-like appearance (Fig. 31.16).[109] It can also be confused with sarcoma (particularly leiomyosarcoma) and sarcomatoid carcinoma. Immunohistochemically, there may be reactivity for low-molecular-weight keratin, which may contribute to the misinterpretation of the lesion. Clues to its recognition are the distinctly fascicular pattern, the Kaposi sarcoma-like areas, fine nuclear chromatin, the absence of pleomorphism, the fact that the mitoses—although abundant—are all typical, and, most important, the history of a recent operation in the area.

Leiomyoma is the most common benign mesenchymal tumor of the vagina.[108,111] The patients are adults, and any region of the vagina can be affected. A peculiar case has been seen containing paraganglioma-like tissue within.[112]

Leiomyosarcoma can attain a large size and ulcerate.[113] The majority of the cases manifest their malignancy only through local recurrence. The criteria of malignancy used by Tavassoli and Norris[111] were the presence of moderate to marked atypia and five or more mitotic figures per 10 high-power fields. Poorly differentiated tumors are associated with a high mortality rate.[114]

Rhabdomyoma presents as a polypoid mass.[115] All of the reported cases have occurred in adult patients, an important differential point with botryoid rhabdomyosarcoma, discussed later. Microscopically, the lesion consists of interweaving and haphazardly oriented

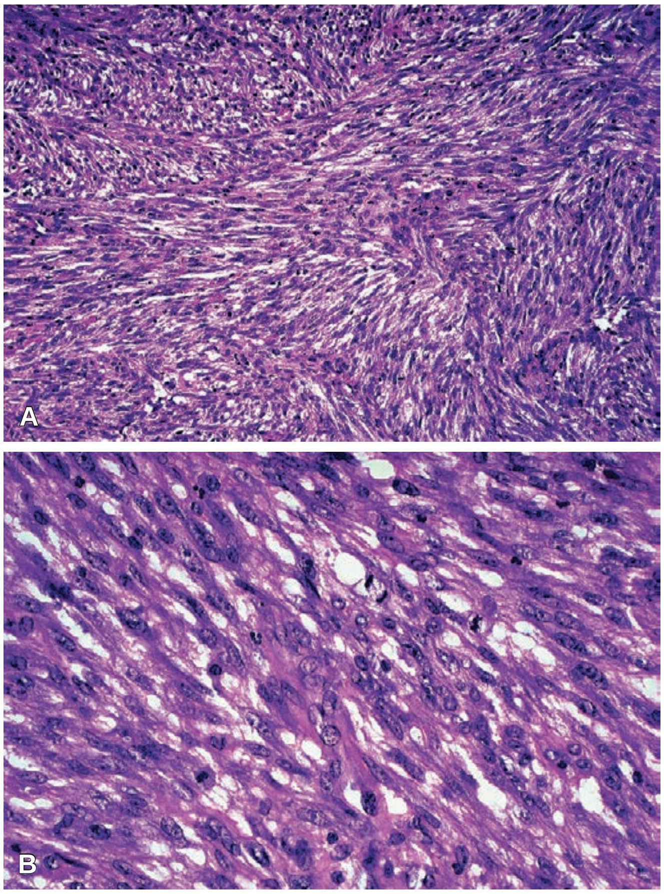

Figure 31.16 **A** and **B,** Medium- and high-power views of postoperative spindle cell nodule. The lesion is extremely cellular and mitotically active, but there is little pleomorphism.

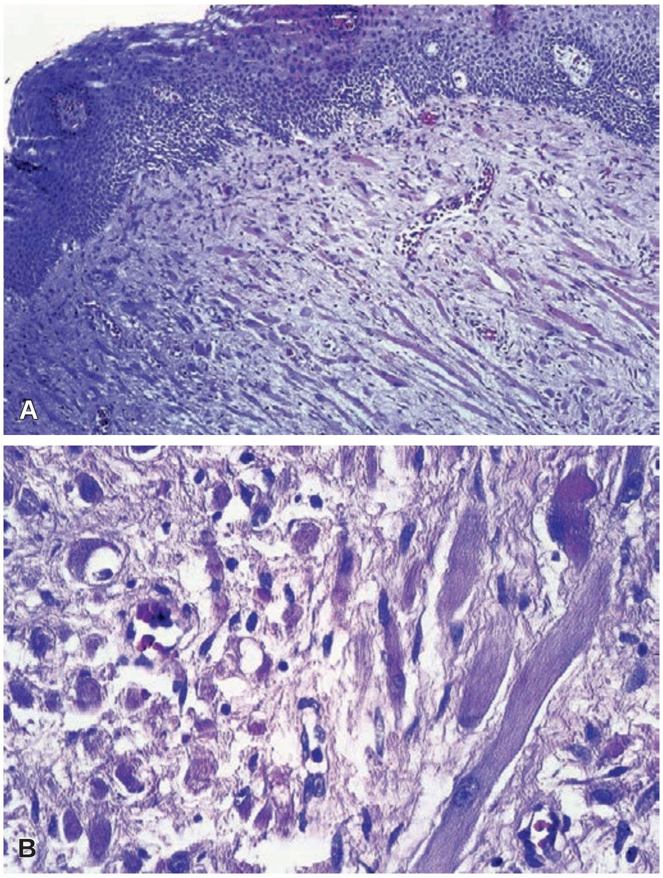

Figure 31.17 **A** and **B,** Vaginal rhabdomyoma composed of bundles of mature skeletal muscle cells scattered in the stroma beneath normal squamous epithelium.

bundles of spindle- to strap-shaped cells, some with cross striations (Fig. 31.17).[116] Mitoses are scanty or absent, and there is no concentration of neoplastic cells beneath the epithelium.

Other benign mesenchymal tumors that have been reported in the vagina are *hemangioma, hemangiopericytoma,*[117] *glomus tumor,*[118] *benign "triton" tumor,*[119] *angiomyolipoma,*[120] *(cellular) schwannoma,*[121] and *neurofibroma.*[122]

Embryonal rhabdomyosarcoma (sarcoma botryoides) is a rare polypoid invasive tumor that usually arises from the anterior vaginal wall (Fig. 31.18).[123] Approximately 90% of cases occur in girls under 5 years of age, with close to two-thirds appearing during the first 2 years. Grossly, it presents as a conglomerate of soft polypoid masses resembling a bunch of grapes—hence its designation as "botryoid."

Microscopically, a myxoid stroma is seen containing a mixture of fusiform, round, or spindle cells (Fig. 31.19). Some of these cells contain a bright eosinophilic granular cytoplasm suggestive of rhabdomyoblastic differentiation. Their racquet- or strap-shaped form mimics that of the cells seen during normal muscle embryogenesis. Cross striations may or may not be present. An important diagnostic feature is the crowding of the tumor cells around blood vessels and, most important, beneath the squamous epithelium. The latter results in a distinctive subepithelial dense zone (the "cambium layer" of Nicholson) (Fig. 31.20). Invasion of the overlying epithelium can be seen. Foci of neoplastic cartilage may be found; these tend to occur in older patients and/or in tumors located higher in the vagina or cervix, and they are said to be associated with a better prognosis. Botryoid tumors are currently regarded as a variation in the growth pattern of embryonal rhabdomyosarcoma, due to their location immediately beneath an expansile epithelial lining. They cause death more often by direct extension than by distant metastases.[124] Of the 15 autopsied cases reviewed by Hilgers et al.,[125] the tumor was confined to the pelvis in about half.

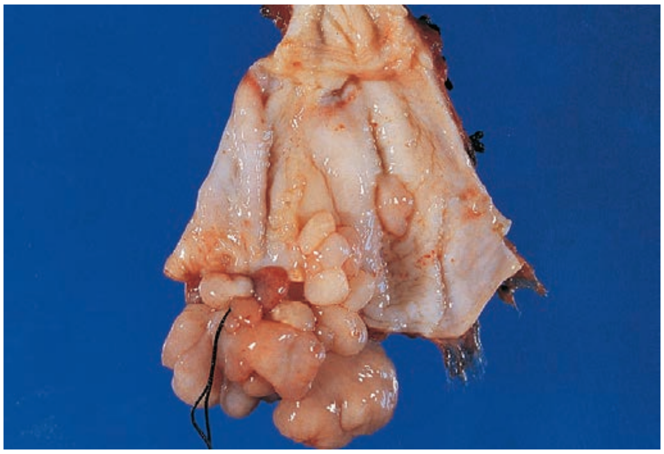

Figure 31.18 **Botryoid Embryonal Rhabdomyosarcoma of Vagina.** The grape-like configuration of this lesion is characteristic.

The treatment of this tumor, traditionally consisting of radical surgery,[126,127] is now primarily based on chemotherapy, which can

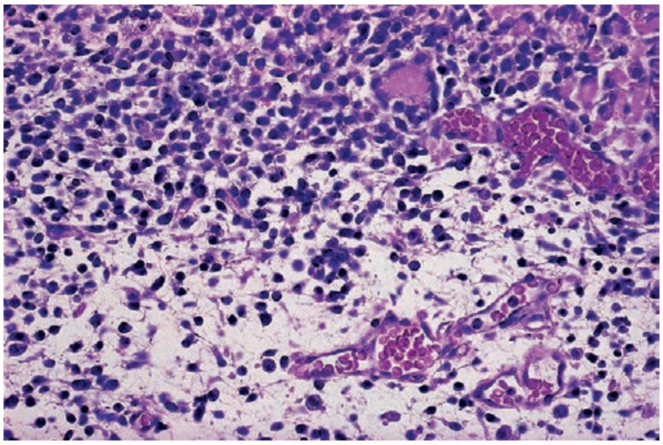

Figure 31.19 **Microscopic Appearance of Embryonal Rhabdomyosarcoma.** The differential diagnosis is that of small round cell tumors.

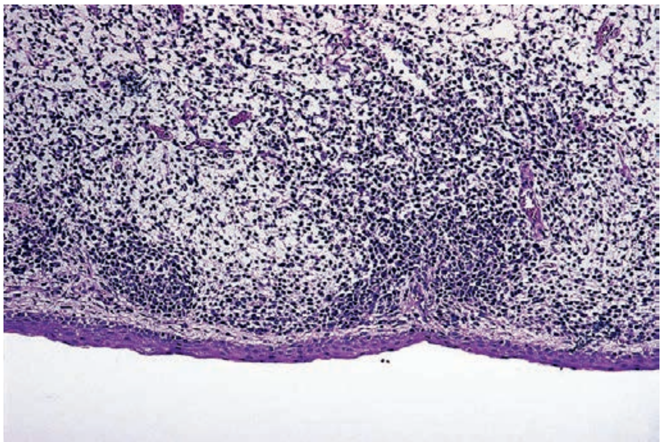

Figure 31.20 So-called cambium layer beneath non-neoplastic epithelium in embryonal rhabdomyosarcoma.

be combined with radiation therapy and/or surgery depending on the circumstances.[128]

Other primary sarcomas that have been reported in the vagina are *stromal sarcoma* of endometrial type,[129] *malignant peripheral nerve sheath tumor*,[129] *angiosarcoma*[130] (sometimes arising as a complication of radiation therapy[131]), *alveolar soft part sarcoma*,[132–134] synovial sarcoma,[135] and Ewing sarcoma/PNET.[136] Confirmation of the characteristic molecular abnormalities, where available (e.g., EWS translocation in Ewing sarcoma), is key to accurate diagnosis of these rare sarcomas.

Melanocytic Tumors

Melanoma can occur as a primary vaginal tumor in elderly patients.[137–140] It presents as a soft polypoid mass, blue or black, and frequently ulcerated (Fig. 31.21).[141] Most cases are located in the lower one-third and in the anterolateral aspect.[142] Microscopically, the appearance is similar to that of the cutaneous melanomas, although they tend to show greater anaplasia and pleomorphism (Fig. 31.22). An intraepithelial component of lentiginous appearance should be looked for to substantiate a local origin, although this feature can be destroyed by the tumor ulceration. The prognosis is extremely poor.[138,143,144] BRAF and KIT mutations were not identified in a series of primary vaginal melanomas, but 12% of cases had NRAS mutations and another 12% had KIT amplification.[145] The melanocytes that have been identified in 3% of normal vaginas[139] most likely represent the cell of origin of this neoplasm, sometimes through a preceding stage of melanosis or atypical melanocytic hyperplasia.[146,147]

Blue nevus of the ordinary type can present as a primary vaginal lesion.[141]

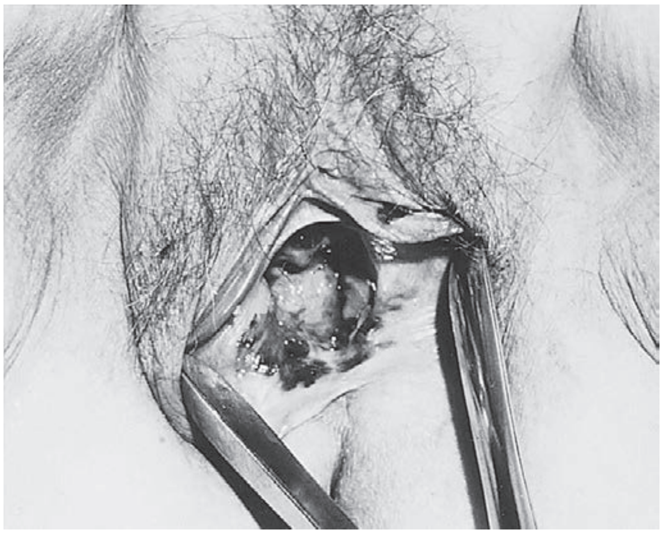

Figure 31.21 Malignant Melanoma of Vagina. (From Norris HJ, Taylor HB. Melanomas of the vagina. *Am J Clin Pathol*. 1966;46:420–426.)

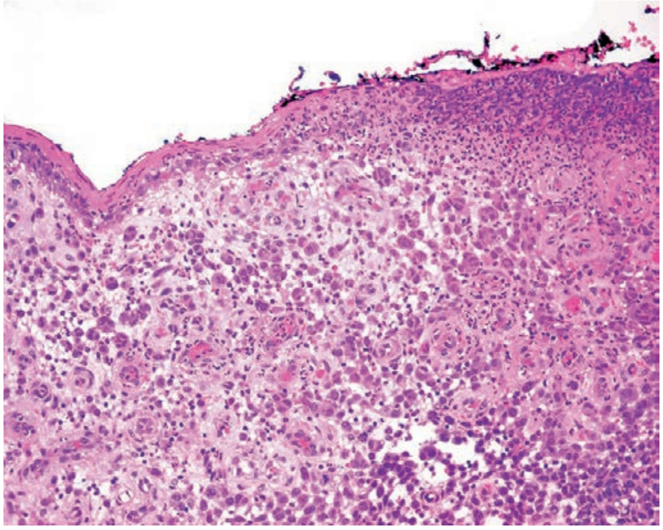

Figure 31.22 **Malignant Melanoma of Vagina.** The tumor has an undifferentiated appearance, is largely amelanotic, and has an ulcerated surface.

Other Primary Tumors

Yolk sac tumor (endodermal sinus tumor) typically affects infants under 2 years of age and is more commonly located in either the posterior wall or the fornices.[148,149] Clinically, it can simulate rhabdomyosarcoma.[150] Microscopically, the most important differential diagnosis is with clear cell (adeno)carcinoma, a tumor with which it has been confused in the past. Immunohistochemically, reactivity for SALL4 and alpha-fetoprotein favors yolk sac tumor, and reactivity for Leu-M1 favors clear cell carcinoma.[151] In early series, most patients with vaginal yolk sac tumor died with generalized metastases,[152] but the combination of surgical excision and multidrug chemotherapy (sometimes with the addition of radiation therapy) has resulted in many long-term cures.[129,153]

Malignant lymphoma can affect the vagina secondarily or sometimes as the only site of involvement; nearly all cases are of non-Hodgkin type.[154–156] The largest group is represented by diffuse large B-cell lymphomas.[157] A case has been reported in association with malakoplakia.[158] Vaginal involvement can also occur in *acute myeloid leukemias* (granulocytic sarcoma).[159]

Other primary tumors of the vagina or paravaginal region, all exceptionally rare, are *Brenner tumor*,[160,161] *female adnexal tumor of probable wolffian origin*,[162] *PEComa*,[155] *myoepithelioma*,[163] and *gastrointestinal stromal tumor* (presenting in the vaginal wall or in the rectovaginal septum).[164,165]

Metastatic Tumors

Metastatic carcinoma to the vagina arises most commonly in the uterine cervix and endometrium, followed by the ovary, large bowel, and kidney.[166–168] Some cases represent direct extension, and others are distant metastases. The metastases from endometrial adenocarcinoma are often submucosal and located in the upper third of the organ.

Other tumors that can metastasize to vagina are melanoma[169] and malignant trophoblastic neoplasms, including epithelioid trophoblastic tumor.[170]

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32

Uterus: Cervix

Blake Gilks

CHAPTER CONTENTS

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Normal Anatomy

The cervix is the lower portion of the uterus which connects this organ to the vagina through the endocervical canal. It is divided into a portion that protrudes into the vagina *(portio vaginalis)* and one that lies above the vaginal vault *(supravaginal portion)*. The outer surface of the portio vaginalis is known as the exocervix or ectocervix, and the portion related to the endocervical canal corresponds to the endocervix. The opening of the endocervical canal onto the exocervix is known as the *external os*, whereas the grossly indistinct upper limit of the endocervical canal is designated the *internal os*.[1]

Most of the exocervix is covered by nonkeratinizing squamous epithelium that in childbearing age is composed of three layers: basal cell, midzone (stratum spongiosum), and superficial. The portion of the midzone immediately above the basal layer is referred to as the *suprabasal layer*. The morphologic appearance of the various layers varies with age; in the postmenopausal period, the cells are atrophic and exhibit a high nuclear-to-cytoplasmic ratio. These changes should not be misinterpreted as evidence of squamous intraepithelial lesions (SILs)/cervical intraepithelial neoplasia (CIN).

Histochemically, the cells above the basal layer show variable amounts of glycogen, readily appreciated in sections with a periodic acid–Schiff (PAS) stain and clinically by the application of the iodine (Lugol or Schiller) test. Immunohistochemically, the cells of the basal layer are positive for low-molecular-weight keratin and tissue polypeptide antigen (TPA) but not for high-molecular-weight (epidermal type) keratin or for involucrin.[2–6] The latter two markers become positive in the cells above the basal layer. Basal cells are also immunoreactive for estrogen receptors.[7]

The glandular mucosa of the endocervix is formed by a layer of columnar mucus-secreting cells, the histochemical reactivity for the mucin depending on the time of the menstrual cycle.[8] These cells rest on a normally inconspicuous layer of subcolumnar “reserve” cells, which are also positive for TPA.[2] These “reserve” cells (in particular, those located at or near the squamocolumnar junction) are primarily involved in the processes of squamous metaplasia, high-grade squamous intraepithelial lesion (HSIL) (CIN2/3), and carcinoma. The glandular epithelium is immunoreactive for estrogen receptors.[7] In addition to lining the surface, it invaginates into the stroma to produce elongated clefts (usually <5 mm deep but sometimes as deep as 1 cm or more), forming the endocervical glands.

The area where the squamous and glandular epithelia meet is known as the *squamocolumnar junction* (Fig. 32.1). It should be noted that this junction is not located in the anatomic external os but rather in the adjacent exocervix, a fact that renders it easily accessible to the colposcope. The portion of endocervical mucosa covering the exocervix is sometimes referred to as *ectropion* and, inaccurately, as *erosion*. This is a very unstable region, in which replacement of one epithelium for another repeatedly occurs, a process that Robert Meyer allegorically referred to as “the fight of the epithelia.” Today, this area is more prosaically known as the *transformation zone*.

Scattered endocrine cells are found in both the normal endocervix and exocervix,[9,10] and melanocytes are occasionally detected along the exocervical basal layer.[11]

The stroma of the cervix is mainly made up of fibrous tissue admixed with elastic fibers and scattered smooth muscle fibers. It has a dominant CD34 immunophenotype, whereas the endometrial stroma has a dominant CD10 phenotype.[12]

Remnants and Ectopias

Mesonephric rests are remnants of the wolffian ducts that are found surrounded by the endocervical stroma in about a third of women.

Abstract

Diseases of the uterine cervix account for a burden of human suffering and mortality that is disproportionate to its size, due to the susceptibility of the epithelium of the cervical transformation zone to infection by oncogenic human papilloma virus (HPV). Despite the introduction of cervical screening programs, cancer of the cervix remains one of the most common cancers. With the introduction of vaccination against HPV it can be anticipated that there will be a decrease in the number of surgical pathology specimens taken for evaluation of primary diseases of the cervix, but this is years off and in the near term, the pathology of the cervix will be important in any general surgical pathology practice.

Keywords

cervix,
HPV,
HSIL,
LSIL,
CIN,
squamous cell carcinoma,
adenocarcinoma

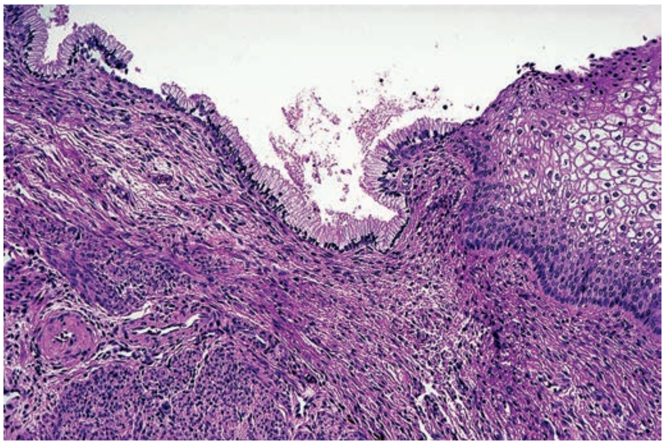

Figure 32.1 Transition zone of uterine cervix between exocervical squamous cells and endocervical mucin-producing glandular epithelium.

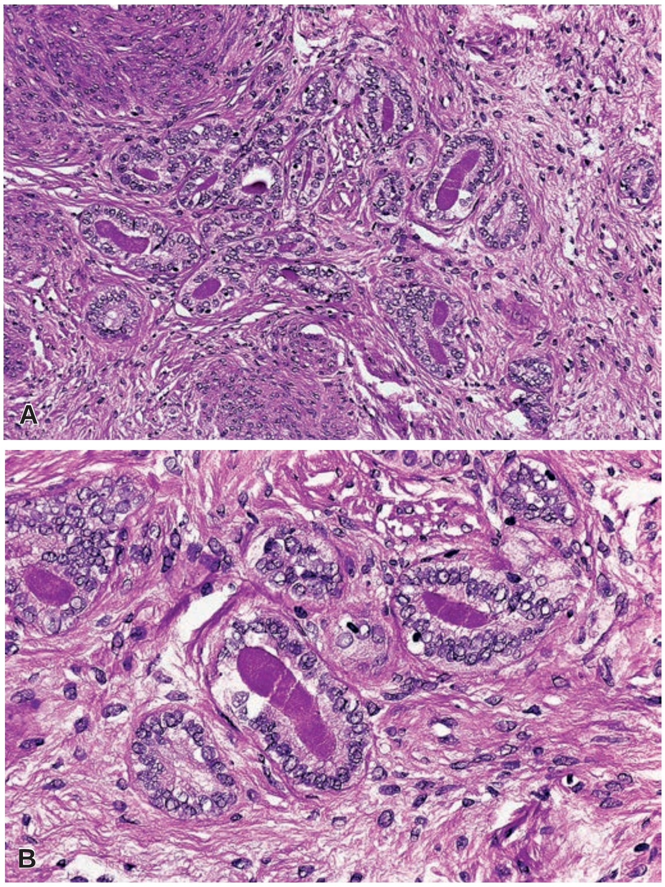

Figure 32.2 **A** and **B**, Florid mesonephric rests in endocervix. Note the eosinophilic inspissated secretion in the glandular lumen, an important diagnostic clue.

They are composed of tubules lined by a single row of cuboidal cells; they typically contain an inspissated deeply eosinophilic secretion in the lumen (Fig. 32.2). They are immunoreactive for PAX8, PAX2, and GATA3, a fact potentially useful for their distinction from endocervical adenocarcinoma and other glandular proliferations of the cervix.[13,14]

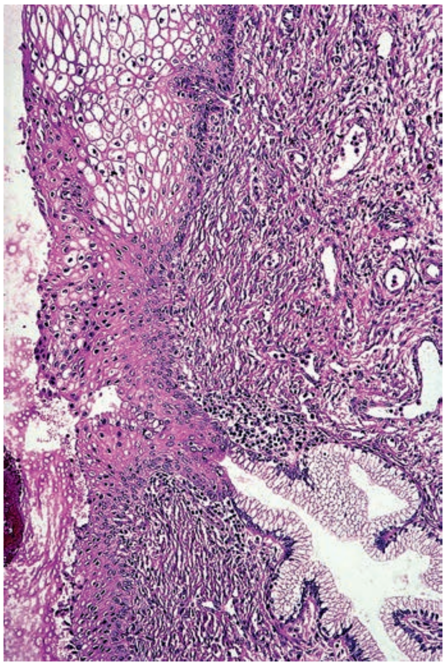

Figure 32.3 Squamous metaplasia of endocervix involving surface epithelium and glandular opening.

Ectopic tissues sometimes found in the cervix include *cutaneous adnexa* (sebaceous glands and hair follicles),[15] *prostatic tissue* (sometimes referred to as "female prostate"),[16–18] and *mature cartilage islands*.[19] The latter (which may be metaplastic rather than ectopic) should not be confused with the cartilaginous component of a carcinoma or a rhabdomyosarcoma.

Squamous and Other Metaplasias

Various types of metaplastic change of the cervical epithelium occur, their appearance being related to the type of mucosa affected. Squamous metaplasia, by far the most common (to the point that some regard it as a normal finding) is centered on the transformation zone; transitional metaplasia involves the exocervical squamous epithelium; and tubal, tuboendometrial, and intestinal metaplasia affect the glandular epithelium of the endocervix.

The term **squamous metaplasia** is used to designate the focal or extensive replacement of the mucus-secreting glandular epithelium by stratified squamous epithelium, which, in its late stage, is morphologically indistinguishable from the epithelium normally lining the exocervical portion (Fig. 32.3). The pathogenesis of this process, also known as *prosoplasia*, has been a subject of a heated controversy over the years. It is now generally agreed that it most commonly arises on the basis of proliferation and metaplasia of reserve cells. It is possible that in other instances it results from direct ingrowth of mature native squamous epithelium into the endocervical mucosa from the exocervix, possibly as a healing mechanism of a true cervical erosion.[20] Strictly speaking, the latter is not a metaplastic process but rather one of "squamous epithelialization." However, it is common usage to employ the term squamous metaplasia regardless of the presumed mechanism for the change.

Some degree of squamous metaplasia is present in almost every uterine cervix during the childbearing years. Most commonly, the process involves only the superficial epithelium and is recognized by the presence of squamous epithelium overlying endocervical glands. In other instances, it involves the glandular component as

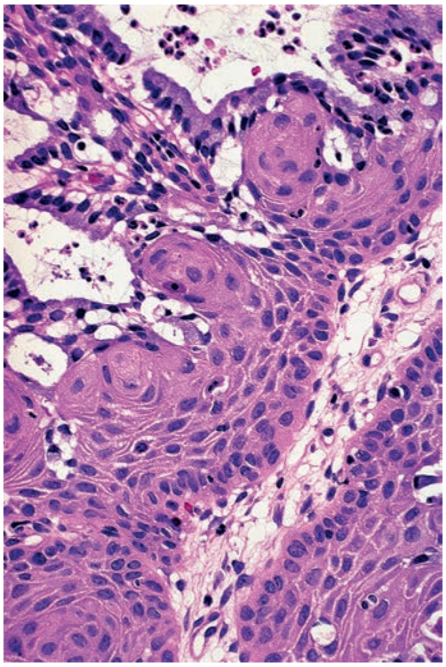

Figure 32.4 Complex pattern resulting from cervical squamous metaplasia. It may result in an overdiagnosis of squamous cell carcinoma.

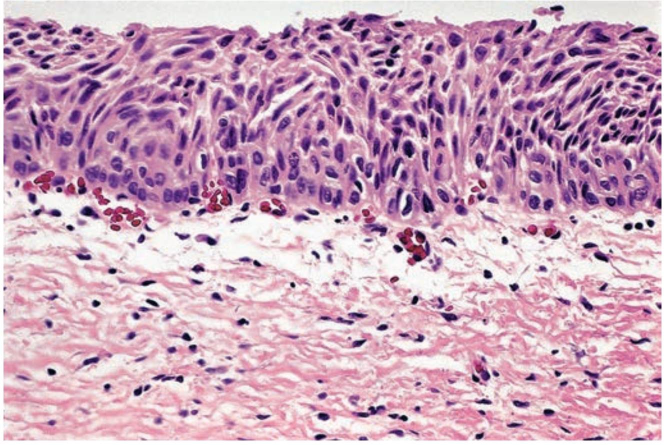

Figure 32.5 Typical appearance of transitional metaplasia, which lacks the nuclear atypia of HSIL (CIN2/3).

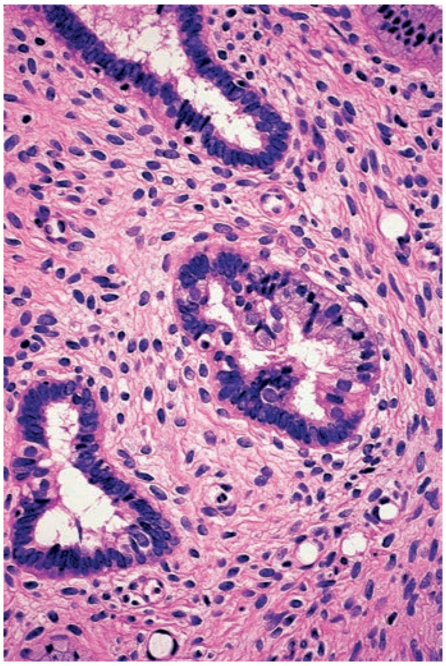

Figure 32.6 Tubal metaplasia of endocervix. Some of the lining cells are ciliated.

well, resulting in a complex microscopic appearance that can be confused with invasive carcinoma by the inexperienced (Fig. 32.4).

Ultrastructural and immunohistochemical markers of squamous epithelium appear *pari passu* with the morphologic changes.[21,22] Variations on this theme, probably representing various stages within a continuum, have been described as *reserve cell hyperplasia* and as *immature, intermediate*, and *mature squamous metaplasia*.[23] The presence of cytologic atypia in immature squamous metaplasia raises the possibility of SIL/CIN; p16 immunostaining can be used to establish a diagnosis of HSIL (CIN2/3), but there remains significant overlap in the morphologic features between atypical immature metaplasia and low-grade squamous intraepithelial lesion (LSIL), with resulting interobserver variability in distinguishing between these two possibilities.[23–28] The diagnosis of SIL is discussed in more detail later in this chapter.

All of the above changes are characterized by a flat architecture and are, therefore, different from the condyloma and other papillary processes, including so-called papillary immature metaplasia (immature condyloma).

Although most cervical carcinomas arise in areas of the cervix that sometime in the past had been involved by squamous metaplasia, the latter process has no premalignant connotations per se. Actually, it is so common and insignificant that, unless quite extensive and/or involving the glandular component, we tend to ignore it altogether in our pathology reports.

A somewhat different appearance is seen often in the cervix of prolapsed uteri. The clinical appearance is usually referred to as "leukoplakic." Microscopically, the process involves mainly the exocervical portion and is characterized by the appearance of granular and horny layers in the epithelium. This process, which is also unrelated to carcinoma, is best designated as *keratosis*. Sometimes this epithelium contains scattered large pale cells, a change that has been dignified by the term *pagetoid dyskeratosis*.[29]

Transitional metaplasia is seen in the exocervix of older women, and it is often associated with atrophy. It morphologically resembles transitional (urothelial) epithelium, and it involves the entire thickness of the mucosa, without evidence of normal squamous maturation. The nuclei are oval and devoid of atypical features. Their long axes, which are arranged perpendicularly to the surface, often exhibit longitudinal grooves (Fig. 32.5).[30,31] Immunohistochemically, there is positivity for CK13, CK17, and CK18 but not for CK20.[32] Its phenotypic profile is very similar to that of senile atrophy.[33] Although this entity has engendered some controversy in the past, with respect to its relationship to SIL,[34] it is now regarded as an entirely benign metaplastic change that differs from atrophy only in consisting of a greater number of cellular layers.[35,36]

Tubal metaplasia is diagnosed when a specimen from the endocervix (usually from the upper portion) is found to contain all three cell types found in the normal fallopian tube (i.e., ciliated, secretory, and intercalated; Fig. 32.6).[37,38] In many instances, the appearance of the metaplastic epithelium combines features of tubal and endometrial mucosa, in which case the term *tuboendometrial* *(tuboendometrioid) metaplasia* is employed.[39–41] Diagnostic difficulties may result from the fact that these glands may be deeply seated, irregularly shaped, cystically dilated, and/or accompanied by a hypercellular, edematous, or myxoid stroma.[42] The condition can be identified in cytologic preparations.[43]

Combined staining for Ki-67 and p16 is of help in the differential diagnosis from in situ and invasive endocervical adenocarcinoma, as tubal metaplasia shows a lower proliferative index and lacks the strong, diffuse, block positivity for p16 seen in human papilloma virus (HPV)-associated adenocarcinomas.[40,44] Tubal metaplasia is often found after conization, and it has therefore been suggested that it represents aberrant differentiation following injury.[45]

A *pseudoinvasive* form of the condition has been described in women with a history of in utero diethylstilbestrol (DES) exposure, suggesting that it may be a form of DES-related adenosis.[46]

Intestinal metaplasia is a vanishingly rare condition, which may be accompanied by extravasation of mucin into the stroma.[47] The presence of goblet cells in the endocervix should prompt a search for dysplastic change/adenocarcinoma in situ; this may be HPV associated or HPV independent.

Oxyphilic (eosinophilic) metaplasia is characterized by the presence of large cuboidal or polygonal epithelial cells with dense eosinophilic, focally vacuolated cytoplasm and variable nuclear atypia in the endocervical glands.[48,49] The differential diagnosis includes HSIL (CIN2/3) with eosinophilic cells, which can be recognized based on the presence of mitotic activity and p16 immunoreactivity.[49]

Inflammatory Lesions

Chronic cervicitis is an extremely common condition in adult females, at least at the microscopic level. It affects preferentially the squamocolumnar junction and endocervix, and it may be accompanied by hyperemia, edema, fibrosis, and metaplastic changes in the epithelium. The etiology is variable.[50] In most cases the disease is asymptomatic. Given that the presence of inflammatory cells at the squamocolumnar junction is normal (this being the junction between the sterile endometrial cavity/endocervix and the exocervix/vagina), it is a highly subjective distinction between "normal cervix" and a degree of inflammation that merits designation as "chronic cervicitis."

Herpes simplex infection of the cervix is now recognized as a relatively common occurrence. The microscopic appearance at the time of biopsy is usually that of an intense nonspecific inflammation with ulceration (Fig. 32.7A). Only rarely are diagnostic multinucleated squamous cells with intranuclear inclusions encountered (see Fig. 32.7B).[51] The diagnosis can be confirmed by immunocytochemical demonstration of the viral antigen.[52,53]

***Chlamydia trachomatis* infection** is now recognized as the most common venereal disease in the Western world. The microscopic appearance in the cervix is that of a chronic nonspecific inflammation, with reactive epithelial atypia and sometimes prominent formation of lymphoid follicles.[54,55] The organisms are not visible in routine histologic slides and only with difficulty in cytologic preparations, but they can be detected by immunocytochemical techniques.[55] Culture isolation is regarded as the standard for diagnosis of active infection. Chlamydial cervicitis can be associated with CIN, but there is no evidence of a causal relationship.[56]

Syphilis can affect the cervix, usually in the form of a primary chancre.[57]

Amebiasis may produce a polypoid and ulcerated mass in the cervix clinically simulating carcinoma, and it may also engraft itself upon a preexisting cervical carcinoma.[58,59]

Actinomycosis of the cervix occurs, but it needs to be distinguished from the more common pseudoactinomycotic radiate granules that may form around microorganisms or biologically inert substances.[60]

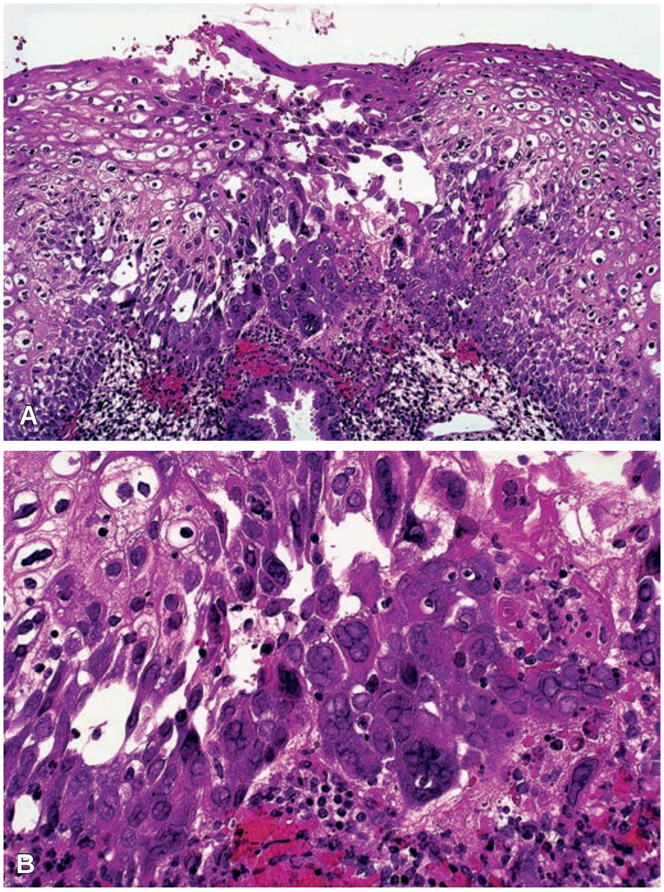

Figure 32.7 **A** and **B**, Low- and high-power appearance of herpes simplex infection of cervix. Multinucleated epithelial cells and intranuclear inclusions are evident in the high-power view.

Bilharziasis (schistosomiasis), common in Africa and Central America, can involve any portion of the female genital tract, including the cervix.[61]

Malakoplakia occurs rarely in the cervix, sometimes in association with disease in the uterine corpus, renal pelvis, or kidney.[62]

Ceroid granuloma of the type more commonly seen in the gallbladder has, exceptionally, been found to involve the cervix.[63,64]

Localized arteritis of the cervix has been described, accompanied by inflammation and ulceration, and apparently restricted to this anatomic site.[65,66] The cervix can also be involved in cases of granulomatosis with polyangiitis (formerly known as Wegener granulomatosis).[67]

Non-Neoplastic Glandular Lesions

Endocervical polyps are not true neoplasms but are probably the result of chronic inflammatory changes ("chronic polypoid cervicitis"). They are usually small but may reach several centimeters in diameter. Microscopically, dilated endocervical glands are seen in an edematous, inflamed, and fibrotic stroma. HSIL (CIN2/3) is an occasional incidental finding in a polyp. Occasionally, the configuration of these polyps is that of a branching papillary structure, in which case the term *papillary endocervicitis* is employed (Fig. 32.8).[47] This lesion is to be distinguished from so-called superficial cervicovaginal myofibroblastoma, which is equally benign and perhaps histogenetically related.[68] Exceptionally, cells with the morphology of signet

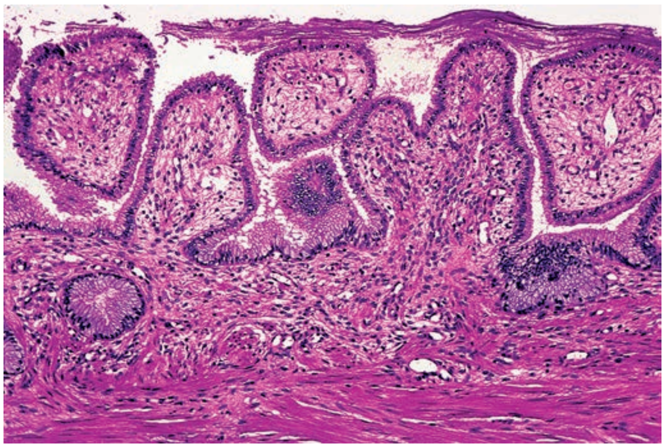

Figure 32.8 Chronic endocervicitis resulting in a papillary configuration at the surface. This pattern is sometimes referred to as papillary endocervicitis.

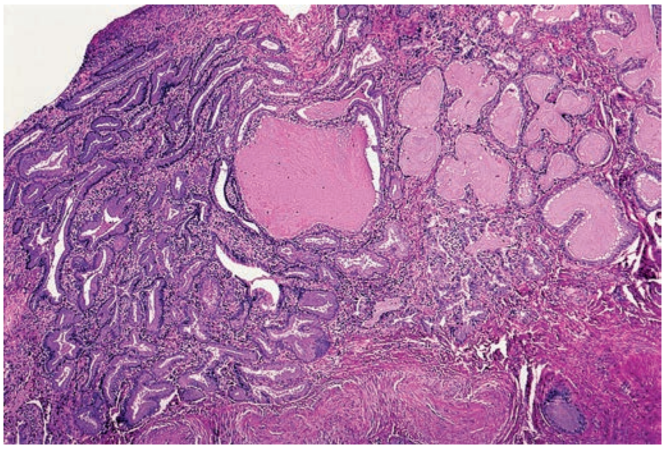

Figure 32.9 Cervical tunnel clusters of predominantly cystic type.

ring cells are seen within an ulcerated endocervical polyp; they are probably the result of ischemia and should not be overdiagnosed as signet ring cell carcinoma.[69]

Nabothian cysts are thought to develop from blockage of the endocervical glands secondarily to inflammation and associated changes; they appear grossly as cystic spaces filled with mucoid material and microscopically as cystically dilated glands lined by a flattened epithelium, sometimes focally absent. Occasionally they extend deeply into the cervical wall, a phenomenon that should not be mistaken for malignancy.[70]

Tunnel clusters, as originally described by Fluhmann, are the result of localized proliferation of endocervical glands (clefts), with side channels growing out from them. This may be accompanied by dilation resulting from the accumulation of inspissated, deeply eosinophilic secretion in the lumen (Fig. 32.9).[71]

Microglandular hyperplasia of the endocervical epithelium was originally described in women using oral contraceptive drugs and, less frequently, during pregnancy.[72,73] However, it can also be seen in the absence of these conditions and even in postmenopausal patients.[74] The relationship between microglandular hyperplasia and oral contraception or other hormonal perturbations has been questioned.[75] Microscopically, the typical case is characterized by a complex proliferation of small glands lined by flat epithelial cells with little or no atypia (Fig. 32.10). The condition usually evolves into squamous metaplasia, resulting in a complex microscopic picture that may be confused with carcinoma (Fig. 32.11). Additional features that may lead to overdiagnosis include areas of solid proliferation, pseudoinfiltrative pattern, signet ring cells, focal atypia, and occasional mitotic figures.[76] The intervening stroma invariably shows chronic inflammation. There is usually no immunocytochemical reactivity for carcinoembryonic antigen (CEA), a useful feature in the differential diagnosis with endocervical adenocarcinoma.[77] Microglandular hyperplasia must be distinguished from endometrial adenocarcinomas with microglandular hyperplasia-like features[78]; these carcinomas are seen in older patients, predominantly within the endometrial biopsy/curettings rather than the endocervical curettings, are often associated with atypical endometrial hyperplasia, and lack the p63 expressing reserve cells present in microglandular hyperplasia.

The **Arias–Stella reaction,** as seen during pregnancy, can involve the endocervical glands. The nuclear abnormalities are similar to

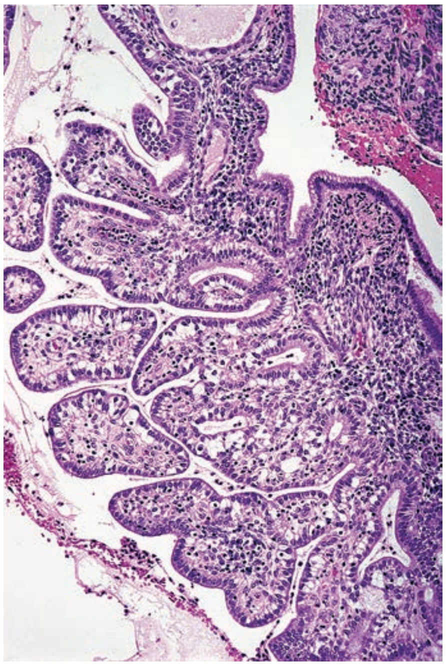

Figure 32.10 Microglandular Hyperplasia of Cervix. The papillary configuration seen here is common in this condition.

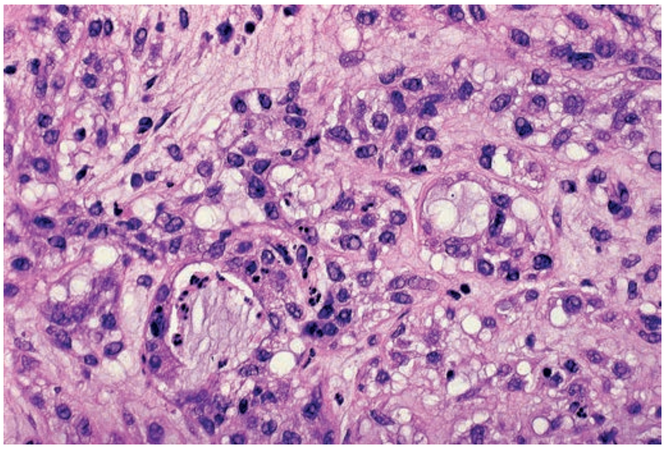

Figure 32.11 Predominantly Solid Form of Microglandular Hyperplasia. This variety is particularly likely to be overdiagnosed as a malignant process.

those seen more commonly in the endometrial mucosa and should not be confused with malignancy.[79–81] The microscopic appearance is quite variable and includes cells with vacuolated clear cytoplasm, intraglandular tufts, hobnail cells, oxyphilic cytoplasm, filiform papillae, nuclear pseudoinclusions, and cribriform intraglandular growth.[82] In contrast to clear cell carcinoma, the Arias–Stella reaction does not form a mass lesion, lacks a desmoplastic stromal response, and does not have an infiltrative pattern.[82]

Atypical reactive proliferation of the endocervical mucosal surface can be seen following endometrial sampling for endometrial carcinoma or other diseases. It shows nuclear stratification, short micropapillary processes, squamous metaplasia, hobnail cells, and mild cytologic atypia (i.e., many of the features that are associated with microglandular hyperplasia). It should not be interpreted as endocervical involvement by an endometrial carcinoma.[83]

Diffuse laminar endocervical glandular hyperplasia (DLEGH) is a non-neoplastic condition characterized by a proliferation of medium-sized, evenly spaced, well-differentiated glands within the inner third of the cervical wall, sharply separated from the underlying stroma, and often accompanied by chronic inflammation (Fig. 32.12)[84]; it should not be confused with adenoma malignum, from which it is distinguishable because of the fact that stromal infiltration, desmoplastic stromal response, and cytologic atypia are absent.[80]

Lobular endocervical glandular hyperplasia (LEGH) is characterized by a distinctly lobular proliferation of small- to medium-sized glands, often centered around a larger central gland.[85] The mucin secreted by some of these lesions is of gastric type.[86] In contrast to adenoma malignum, LEGH lacks irregular stromal infiltration, desmoplastic stromal response, and significant cytologic atypia. Interestingly, the phenotype of this process is similar to that of pyloric glands.[87] A possible pathogenetic relationship between the two conditions (and with HPV-independent mucinous adenocarcinomas of the cervix) has been suggested on the basis of some immunohistochemical and molecular genetic similarities,[87,88] as well as their occasional association.[86,89]

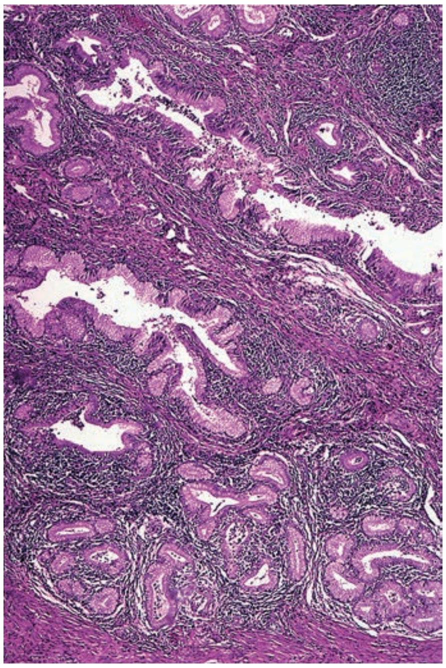

Figure 32.12 **Diffuse Laminar Endocervical Hyperplasia.** The glands are medium sized, evenly spaced, and well differentiated.

Mesonephric duct rests can undergo cystic dilation or be affected by florid and even atypical hyperplastic changes (Fig. 32.13).[90–92] This hyperplasia may have a lobular, diffuse, or ductal pattern (Fig. 32.14).[93] Rare malignant tumors arising from these structures also occur. Mesonephric remnants are also rarely involved by HSIL (CIN2/3).[94] It is doubtful whether the rare benign polypoid lesion found in the cervix and vagina of young children and described as *mesonephric papilloma* is related to these remnants.[95,96] Microscopically, it is a superficially located lesion composed of delicate connective tissue stalks covered by a layer of cuboidal cells and is probably of müllerian derivation.

Non-Neoplastic Stromal Lesions (Including Endometriosis and Related Processes)

Multinucleated stromal giant cells can be present beneath the cervical epithelium and be mistaken for a malignancy. They are often accompanied by edema and may result in a vaguely polypoid-appearing lesion.[97,98] These cells are of a reactive fibroblastic/myofibroblastic nature and analogous to those seen in other sites covered by mucosal membranes, such as vulva, vagina, anus, oral cavity, and nasal cavity.[99,100]

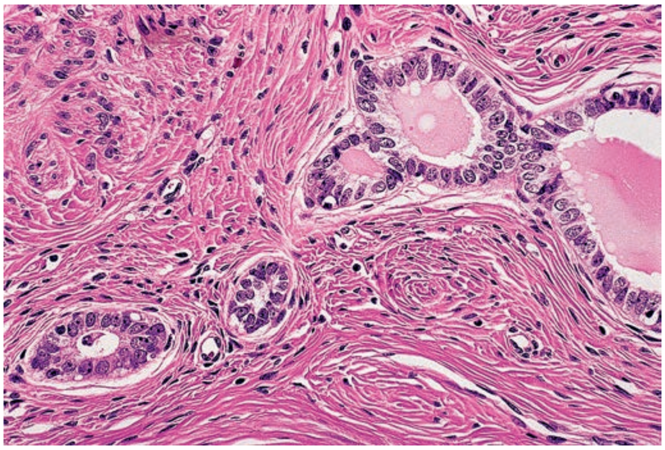

Figure 32.13 Hyperplastic mesonephric rests with mild atypia.

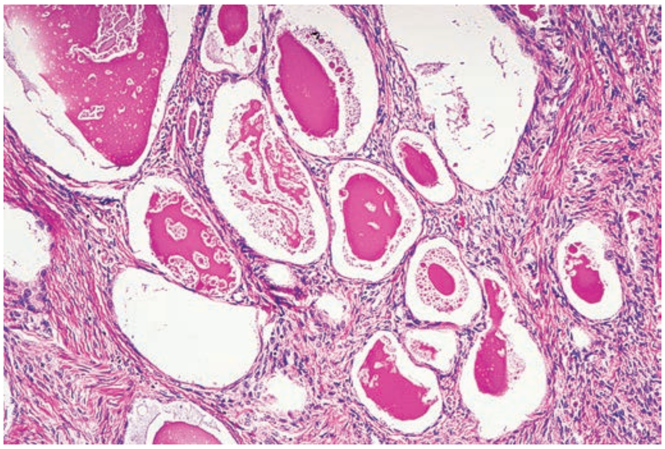

Figure 32.14 Mesonephric glands embedded within the stroma of the uterine cervix exhibiting cystic dilation. The presence of a dense eosinophilic secretion is characteristic.

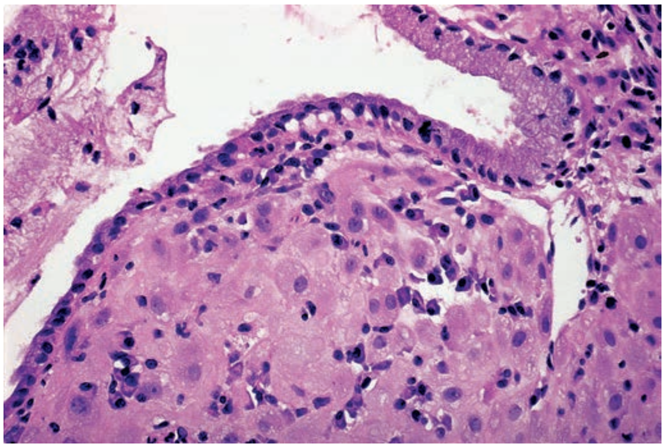

Figure 32.15 Focus of ectopic cervical decidual reaction.

Decidual reaction in the cervix during pregnancy usually presents as multiple, small, yellowish or red elevations of the cervical mucosa. They are soft and friable and bleed easily with trauma. Rarely, they develop into fungating masses difficult to distinguish grossly from carcinoma.[101] Microscopically, the decidual cells are characterized by abundant pale granular cytoplasm and bland nuclei (Fig. 32.15). Immunostains for keratin are negative.

Placental site nodule appears as a well-defined hyalinized lesion located immediately beneath the mucosa.[102] It is composed of intermediate trophoblasts exhibiting cytoplasmic vacuolization.[103,104] Some nuclear atypia may be present. This lesion can be confused with carcinoma and with neoplastic cartilage. Immunohistochemically, the trophoblastic cells are reactive for keratin (another factor that may lead to a mistaken diagnosis of malignancy) but also for human placental lactogen.

Endometriosis of the cervix presents as blue or reddish nodules and may result in abnormal uterine bleeding. Both endometrial glands and stroma are needed to establish the diagnosis. However, the proportion of the two components may vary greatly from case to case. On occasion, the process is composed exclusively of endometrial stroma ("stromal endometriosis") and may be confused with a neoplasm.[105] Another source of confusion arises when the endometriosis is superficial, in which case it may be overinterpreted as endocervical glandular dysplasia or adenocarcinoma in situ, one of the reasons being that it may be mitotically active.[106] It differs from tuboendometrial metaplasia of the endocervix because of the concomitant presence of endometrial-type stroma, however scarce. A lesion with an appearance resembling a miniature uterus in the cervix ("uterus-like mass") has been interpreted as a form of superficial endometriosis with florid smooth muscle metaplasia.[107] A bizarre variation on the theme is represented by **endocervicosis**, which can present as a deep-seated cervical mass simulating endocervical adenocarcinoma.[108]

Necrobiotic granulomas resembling tuberculosis or rheumatoid nodules have been seen following cervical surgery.[109] They are probably histologically and pathogenetically analogous to those described postoperatively in the prostate (see Chapter 26).

Florid mesenchymal reactions can develop from the cervical stroma as a result of various surgical interventions and lead to confusion with sarcoma.[110] Some of these have a nodular fasciitis-like appearance and may be looked upon as the genitourinary equivalent of this soft tissue lesion.

Myxoid changes of probable degenerative nature can sometimes be seen in the cervical stroma (and in the myometrium) in the absence of any other pathology.[111]

Human Papilloma Virus and the Lower Female Genital Tract

The role of HPV in the pathogenesis of both condyloma and carcinoma is so well established that it is easy to forget that relatively recently this relationship was completely unsuspected. It has now been demonstrated that greater than 99% of cervical carcinomas are associated with oncogenic HPV,[112] and the molecular mechanisms of virus-mediated oncogenesis are understood in considerable detail. zur Hausen deservedly won the Nobel prize in 2008 for his work establishing the link between HPV and cervical cancer, and we now see the circle closing, with both primary HPV screening to detect premalignant lesions, and HPV immunization to prevent such lesions increasingly being adopted. Against that background we should acknowledge that this is a rapidly advancing field, and what you read in this section will undoubtedly be out of date prior to the next edition of this text. It is possible to envision a world where the burden of disease due to HPV is dramatically reduced, but that is years away, and for the foreseeable future we will be contending with biopsies and resection specimens where the diagnostic issue is the presence or absence of HPV-associated premalignant changes or malignancy. In the following section we will focus on the biology of HPV, so that we can relate it to histopathologic changes described later.

HPV is a DNA virus and is classified based on the viral genome into different genotypes, each designated by a number (e.g., HPV-6).[113] HPV-2 is the most common cause of verruca vulgaris, but the focus of the following discussion are the genital HPV genotypes, transmitted by sexual contact and associated with either condyloma, in the case of the low-risk HPV genotypes such as 6 and 11, or cervical carcinoma, in the case of the high-risk genotypes (also referred to as oncogenic genotypes, later), of which HPV-16 and 18 are the most important. Other HPV genotypes considered to be oncogenic include 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.[114] Other genotypes are considered to be possibly oncogenic, of uncertain oncogenic potential (i.e., insufficient information to classify), or non-oncogenic; HPV-6 and 11 are in the latter group. Among the oncogenic HPV genotypes, the risk varies, with some being more likely to be associated with malignant transformation.

The genital HPVs are epitheliotropic and the high-risk HPV types, in particular, have a tropism for the metaplastic squamous cells at the squamocolumnar junction.[115,116] This has very important consequences for cytologic screening as most precursor lesions and carcinomas arise at this site, which is amenable to sampling with a brush or spatula. For example, if the lesions of HPV-associated neoplasia of the genital tract were randomly distributed within the squamous mucosa of the vagina and ectocervix, screening would have failed as it has in the oral cavity.

Potentially infectious virus particles must reach the proliferating basal cells for productive infection to take place, and it is thought that a micro-injury to the squamous epithelium is required for this to happen.[117] In the case of glandular epithelium, in which there is a single layer of cells, the proliferating stem cell compartment should, in theory, be more accessible; however, it remains that infection of squamous cells is more likely than the cervical glandular epithelial cells for reasons that are not well understood. Once the virus particles are taken up by the basal epithelial cells the infection may become silent (e.g., through methylation of the viral genome, so that episomic viral DNA remains in the cell but is not transcribed or translated), or productive infection may result. Such an infection may result in orderly expression of viral genes as the host squamous cells mature, with assembly and release of infectious virus particles at the epithelial surface. This is typically associated with koilocytic change, a viral cytopathic effect in which the E4 protein encoded by the viral genome

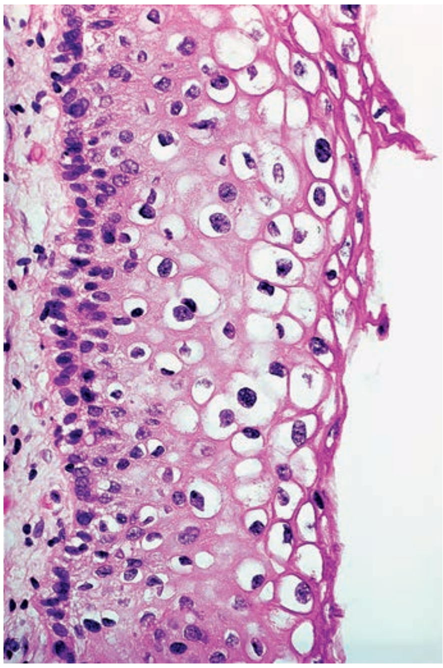

Figure 32.16 Koilocytotic changes in cervical squamous epithelium involved by LSIL (CIN1). These are diagnostic of HPV infection.

causes disruption in the cytoplasmic keratin matrix. The resulting koilocyte is a superficial or intermediate mature squamous cell characterized by a sharply outlined perinuclear vacuolation, dense- and irregular-staining peripheral cytoplasm, and an enlarged nucleus with an undulating (raisin- or prune-like) nuclear membrane and a rope-like chromatin pattern (Fig. 32.16).[118] Binucleation and multinucleation can occur.[119] It is important that these nuclear changes—which may be accompanied by either a diploid or polyploid nuclear DNA distribution[120]—be present somewhere in the lesion for the diagnosis of koilocytosis (and, by inference, HPV infection) to be made, or else other forms of cytoplasmic clearing (notably those related to glycogen accumulation) will be mistakenly included in this category.[121,122] This orderly expression of the viral genome as the squamous cells mature and move to the surface results in LSIL, discussed in more detail later. There may also be, in the case of high-risk/oncogenic HPV infection, deregulated expression of the viral genome. The E6 and E7 proteins encoded by the genomes of these HPV genotypes bind and inactivate the proteins encoded by the *TP53* and *RB* anti-oncogenes, resulting in unfettered proliferation of the host cell. This leads to decreased E4 expression and virion production, and decreased or absent koilocytic change, and increases the likelihood of integration of the viral genome into the host genome, acquisition of other genetic abnormalities in the host cell, and malignant transformation. Not all viral infections lead to transformation and most are cleared by the immune system of the host, through cell-mediated immunity.

HPV can be detected by electron microscopy (as intranuclear crystalline and occasionally filamentous inclusions), but its specific identification depends on nucleic acid hybridization, which can be done with or without amplification, from DNA or RNA, in either a liquid-based or *in situ* analysis.[123–127] Before talking about specific techniques for HPV detection, it is important to reiterate that the presence of HPV DNA may reflect (1) virus particles on the surface of the epithelium secondary to recent exposure, without infection, (2) productive infection that will be cleared completely by the host, (3) a latent infection, or (4) oncogenic HPV DNA that is integrated into the host genome. If the productive infection is by low-risk HPV (6 or 11), it leads to LSIL/condyloma, with viral cytopathic effects, while productive infection with high-risk HPV, most commonly 16 or 18, can lead to LSIL or can progress to HSIL or invasive squamous cell carcinoma. Thus identification of the specific genotype of HPV is of import, but even the identification of high-risk HPV does not mean that there is premalignant change or malignancy, and especially in the young, HPV may be cleared by the host. The Hybrid Capture HPV test, a signal-amplified hybridization microplate-based array designed to detect multiple HPV genotypes, is an example of a liquid based nucleic acid detection technique.[128] These assays are the most sensitive, providing more sensitivity than in situ hybridization techniques. However, they can be too sensitive and may detect virus that has not infected the host or is in the process of being cleared by normal immune mechanisms. Critically for surgical pathology practice, p16 immunohistochemistry has emerged as a highly sensitive and specific surrogate test for infection by high-risk HPV.[129,130] The p16 antioncogene is expressed at high levels in cells due to absence of the normal downregulation of p16 expression by phosphorylated RB protein; in cells infected by high-risk HPV this occurs through inactivation of the RB protein by the viral E7 protein. This results in high-level expression of p16, seen as strong nuclear and cytoplasmic immunoreactivity. There must be "block" positivity for p16 immunostaining to be indicative of high-risk HPV infection (i.e., strong nuclear and cytoplasmic staining of every cell in the basal third of the epithelium), with this staining typically extending into the middle and upper thirds. Correct interpretation of p16 immunostaining is only possible if the staining protocol has been properly validated, and appropriate controls run. There are a number of antibody clones specific for p16, and it is incumbent on each lab to optimize the staining for the clone they have chosen, a responsibility that is sometimes neglected. Immunoreactivity for p16 is not specific for HPV and other tumor types, unrelated to HPV, that have dysregulation of RB can show strong p16 staining (e.g., high-grade serous carcinoma of tubo-ovarian or endometrial origin). p16 expression can be lost through mutation, as cervical cancer progresses, but this appears to be rare in the in situ lesions of HSIL or in situ adenocarcinoma, so that p16 can serve as a very useful surrogate test for high-risk HPV in the cervix. The indications for use of p16 are covered in greater detail later in this chapter. Expression of the viral E5 oncoprotein mRNA is considered a better marker of HPV having a causative role in oncogenesis, in a given case (as HPV DNA may be present as a bystander if there is no transcription of the viral oncogenes), but such testing is currently not widely available in clinical laboratories.

Tumors

Squamous Cell Carcinoma and Its Precursors

Squamous Intraepithelial Lesions/Cervical Intraepithelial Neoplasia

We recommend use of the Bethesda terminology for cytology specimens[131–134] and the diagnostic terminology proposed by the LAST committee,[133] which is based on the Bethesda classification, for surgical pathology specimens. SIL terminology has gained wide acceptance, but there are still holdouts for the CIN terminology and we will adopt the practice, permitted under the LAST recommendations, of providing a two-part diagnosis, with SIL first and the equivalent CIN in parenthesis thereafter. LSIL will thus appear as "LSIL (CIN1)." CIN2 and CIN3 are both considered HSIL, and the distinction between CIN2 and CIN3 is arbitrary and not clinically relevant. Subtle differences in natural history have been reported for CIN2 versus CIN3, but we would attribute these to inclusion in the former group of some cases better classified as CIN1, rather than being an indication that CIN2 and CIN3 are distinct diseases. Accordingly, we will not make an effort to distinguish between CIN2 and CIN3, instead using the terminology HSIL (CIN2/3) for all high-grade lesions.

Most SIL are initially detected cytologically, which leads to colposcopic biopsy. Occasionally SIL will be an incidental finding, sometimes appearing in endometrial biopsy specimens. It is anticipated that there will be a decline in SIL with widespread HPV vaccination, but this has not impacted on practice yet. With primary HPV testing rather than cytologic screening, as discussed in the Cytology section later in this chapter, there will be more patients referred for colposcopic examination, so familiarity with SIL and its mimics will be important for those practicing general surgical pathology for the foreseeable future.

LSIL (CIN1) is inclusive of condyloma in the LAST criteria.[133] The former practice of attempting to determine whether there is or is not dysplasia within condyloma (i.e., condyloma ± CIN1) has mercifully been brought to an end. Koilocytic viral cytopathic effect (see Fig. 32.16) is the pathognomonic feature of condyloma; it is doubtful whether LSIL (CIN1), as an indicator of HPV infection, can be reproducibly diagnosed in the absence of koilocytic change. Condyloma can be exophytic or flat. The former, **condyloma acuminatum**, are considerably less common than the latter and are visible grossly as a polypoid lesion characterized microscopically by papillomatosis, acanthosis, koilocytosis, and a variable degree of inflammatory infiltration of the stroma. An undulating appearance of the epithelium is a characteristic feature on low-power examination. A mild degree of atypia in the squamous component is common and need not be mentioned; if more severe, it should be evaluated and graded as for the flat SIL (i.e., is there HSIL [CIN2/3] present).

Condyloma acuminatum is associated with HPV-6 or HPV-11 in 70%–90% of the cases, but occasionally other types—such as HPV-16—are encountered. When the latter is the case, high-grade cytologic atypia may be found. The differential diagnosis of condyloma acuminatum includes verrucous carcinoma, discussed in more detail later. **Inverted transitional cell (urothelial) papilloma**, similar to its more common bladder counterpart, has been described in the cervix.[127,135] It is probably not related to HPV and is included here only because it enters into the differential diagnosis with the other polypoid benign lesions of this region. Papillary transitional lesions can mimic condyloma acuminatum at low power, but there is no koilocytic change and the cells have very uniform nuclear features, with even chromatin and nuclear grooves. Squamous papilloma is the diagnosis that has been suggested for lesions that architecturally resemble condyloma acuminatum, are composed of benign squamous cells, without dysplasia, but lack koilocytic change. These may be related to condyloma but have cleared the HPV infection, but this is speculative. They are not considered to have premalignant potential.

Flat condyloma, so-called, is more commonly encountered than condyloma acuminatum, and is the classic lesion of LSIL (CIN1). It is typically not recognizable grossly. Microscopically, there is a relatively normal basal cell layer, expanded or hyperplastic parabasal cell layer, orderly maturation, mitotic activity confined to the lower third of the epithelium (but few or no abnormal mitoses), and koilocytosis (Fig. 32.17). A degree of dysplasia of the lower third of the epithelium is acceptable within the spectrum of LSIL, although the distinction between "dysplasia" and reactive expansion of the parabasal layer due to increased proliferation is highly subjective. This lack of ability to distinguish between koilocytic change (HPV effect) with or without dysplasia contributed to them being combined as LSIL in the Bethesda classification. At this point we would most emphatically recommend that the old chestnut that mild, moderate, and severe cervical dysplasia (CIN1-3), respectively, are distinguished by dysplasia in the lower third, lower two thirds, and full thickness of the squamous epithelium be relegated to the bin reserved for medical trivia of historical interest only. This observation is still repeated to trainees and has no underlying mechanistic basis. The Bethesda classification reflects the biology of in situ squamous neoplasia of the cervix, especially as it relates to HPV, with a bipartite LSIL/HSIL system.[134] The proliferation rate of LSIL (CIN1) is higher than that of inflamed or metaplastic cervical squamous epithelium. Most LSIL, apart from condyloma acuminatum, is associated with high-risk HPV types.

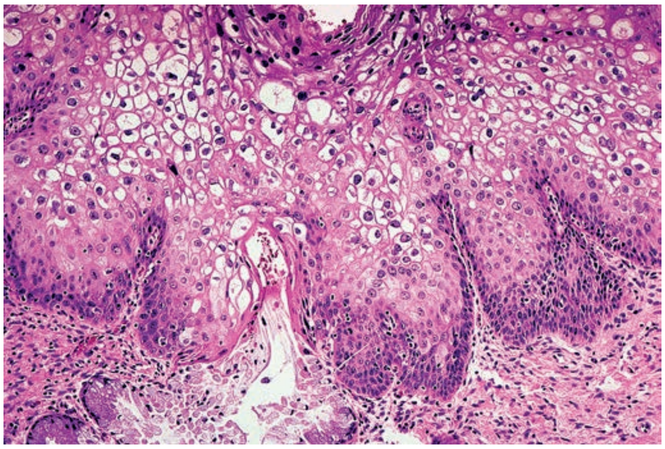

Figure 32.17 HPV-induced LSIL (CIN1) lesion characterized by acanthosis, papillomatosis, and koilocytotic changes.

The natural history of LSIL is that most will clear spontaneously and relatively few will progress to HSIL (CIN2/3). Risk factors for progression include the presence of high-risk HPV, but, as noted previously, high-risk HPV are present in most LSIL. Cytokeratin 7, a marker of squamous cells of the transformation zone, has been proposed as a marker of LSIL that is more likely to progress.[115] This is based on the observation that LSIL/condyloma can arise on the ectocervix or elsewhere in the lower female genital tract and at these other sites there is little risk of progression to HSIL.[115,116] In contrast, the metaplastic squamous epithelium of the transformation zone is especially susceptible to progression when infected by high-risk HPV. CK7 is a marker of these metaplastic cells and, while it shows promise of being a marker of increased likelihood of progression from LSIL to HSIL, further validation is required before it enters routine practice.[136]

HSIL (CIN2/3) may be seen macroscopically, when extensive (Fig. 32.18), but is best appreciated colposcopically. On microscopic examination, it is characterized by a high N:C ratio in all layers of the epithelium, not just the basal and parabasal layers, but most importantly by striking nuclear atypia (Fig. 32.19). There is prominent mitotic activity, with atypical mitoses typically present, and mitotic figures are found in the upper layers of the epithelium. There are cases where the differential diagnosis rests between LSIL and HSIL and the recommendation is that in such lesions p16 immunostaining be used as an adjunct; if there is strong and diffuse block positivity, a diagnosis of HSIL (CIN2/3) can be rendered. It is important to note that diagnosis of LSIL or HSIL is made primarily based on H&E, with use of p16 immunostaining only in selected borderline cases.[129]

At a practical level, HSIL can be safely treated by conization, electrodiathermy, cryosurgery, laser, or loop electrosurgical excision, all of them done under colposcopic guidance.[137–141] In making the final decision regarding the timing and type of therapy for this group

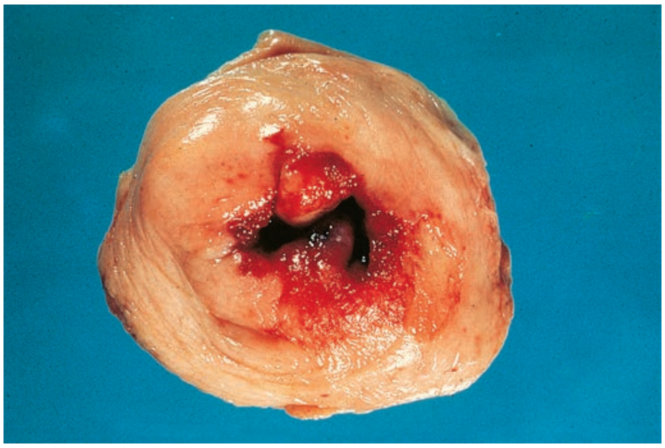

Figure 32.18 Gross appearance of HSIL (CIN2/3) extensively involving the uterine cervix. (Courtesy of Dr Hector Rodriguez-Martinez, Mexico City.)

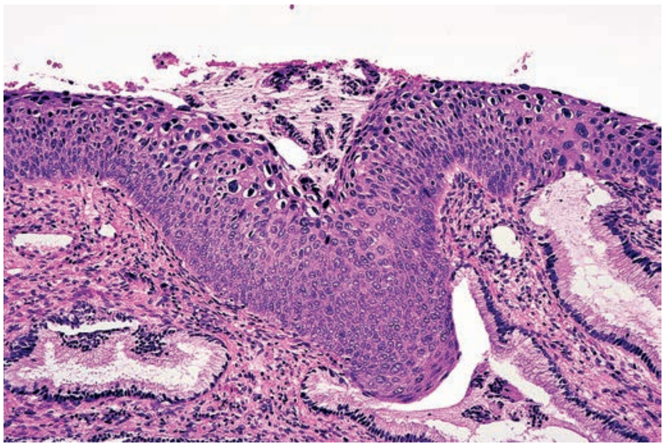

Figure 32.20 Extensive involvement by HSIL (CIN2/3) of surface epithelium and glands of endocervix.

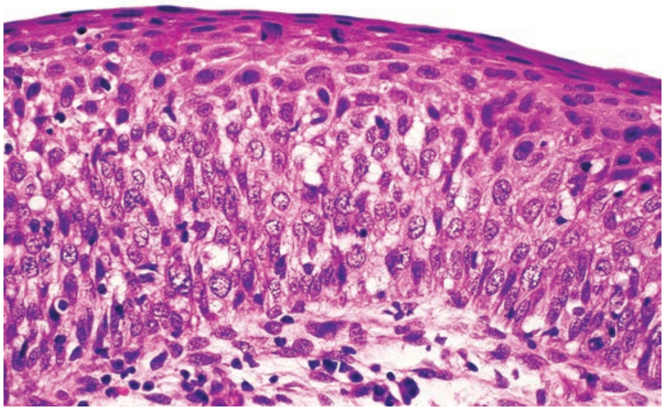

Figure 32.19 HSIL (CIN 2/3). There is proliferation and atypia, with increased N:C ratio and loss of normal maturation.

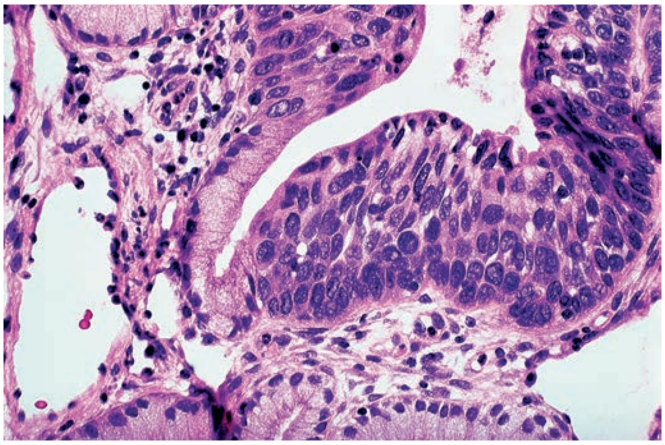

Figure 32.21 Partial replacement of endocervical glandular epithelium by HSIL (CIN2/3).

of lesions, the microscopic diagnosis is only one of the factors to be considered, albeit a very important one. The extension of the lesion, age of the patient, parity, and the desire to have more children all have to be considered. Both the surface and the possible depth of involvement also have to be taken into account, as extension of HSIL (CIN2/3) into endocervical glands is common. (Figs. 32.20 and 32.21) Anderson and Hartley[142] calculated that destruction of tissue to a depth of 2.92 mm would eradicate all involved glands in 95% of the patients, whereas destruction to a depth of 3.8 mm would eradicate 99.7%. Positive margins and glandular involvement by HSIL (CIN2/3) are independent predictors of residual or recurrent disease.[143–145]

Once the pathologist has made the diagnosis of HSIL (CIN2/3) in a cervical biopsy, it is the responsibility of the gynecologist to determine the presence or absence of invasive carcinoma. Thorough cervical sampling and the proper sectioning of tissue should establish whether or not invasive carcinoma exists. If the latter is found, conventional methods of therapy may be instituted. Whenever the therapy is conservative, long-term follow-up (longer than 5 years) is imperative. In one series, patients with continuing abnormal cytology after initial treatment of HSIL (CIN2/3) were found to be 25 times more likely to develop invasive carcinomas than women with normal follow-up cytology.[146]

The differential diagnosis of HSIL (CIN2/3) includes florid squamous metaplasia and transitional metaplasia. It should also be mentioned that the iodine test, used to delineate the extent of cervical disease prior to conization, can induce shrinkage, cytoplasmic eosinophilia and vacuolization, and pyknosis in the epithelial cells (particularly when they are abnormal to begin with).[147]

Superficial Invasive Squamous Cell Carcinoma

Invasive squamous cell carcinomas in which the depth of stromal invasion is minimal (3 mm or less, and <7 mm in breadth, Stage Ia1) have been segregated from the others and designated as “superficial invasive carcinoma” (Fig. 32.22 and Table 32.1).[148–151]

The justification for the recognition of this as a distinct entity is that the natural history of the lesion is quite different from that of ordinary invasive carcinoma and more akin to that of HSIL (CIN2/3).[151–153] Accordingly, the treatment can be generally conservative, although it needs to be individualized.[148,154,155] The common occurrence of pleomorphism, cellular differentiation, presence of conspicuous nucleoli, and individual cell keratinization in the areas of microinvasion has been emphasized (Fig. 32.23).[150] Since these features are rarely seen together in HSIL (CIN2/3), their presence in an apparently intraepidermal cervical lesion should stimulate the

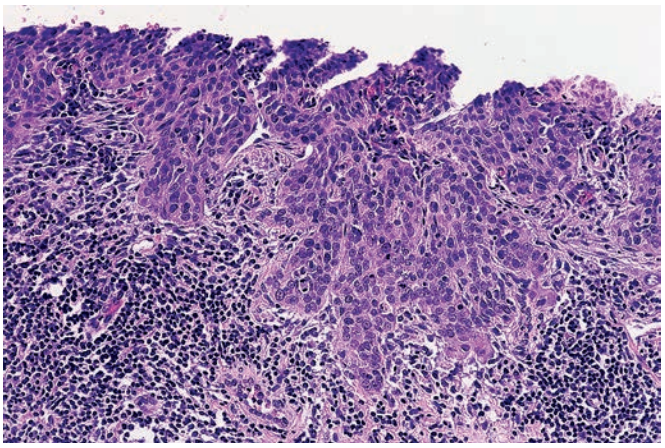

Figure 32.22 Low-power appearance of superficial invasive squamous cell carcinoma of cervix.

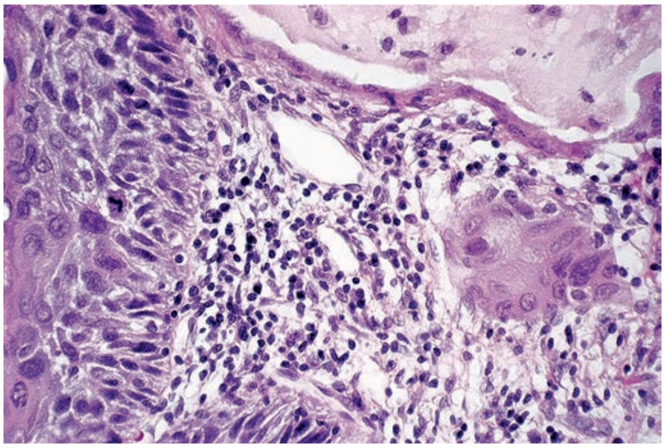

Figure 32.23 Small focus of invasion underlying HSIL (CIN2/3). Note the greater degree of squamous differentiation in the microinvasive component.

search for areas of invasion.[156] Another feature that should raise the suspicion of early stromal invasion is the presence of a desmoplastic stroma rich in acid mucosubstances and characterized by metachromatic staining properties.[157] In the area of invasion, there is a breach of the basement membrane. Hasumi et al.[158] found that one (0.9%) of 106 patients with invasion up to 3 mm had lymph node metastases, whereas four (13.19%) of 29 patients with invasion of 3.1–5 mm had nodal metastases. This study served as the original basis for the definition of superficial invasion as 3 mm or less depth of invasion, with conservative surgery (as for HSIL [CIN2/3]) as treatment of choice, in contrast to the radical surgery, with parametrial and lymph node resection, used for more deeply invasive carcinomas.

Invasive Squamous Cell Carcinoma

General Features

Invasive squamous cell carcinoma of the cervix is still the most common malignant tumor of the female genital tract in most countries and the most frequent neoplasm among women in many of them.[159,160] As noted previously, almost all are HPV associated, but rare HPV-independent squamous cell carcinomas do occur,[161] especially verrucous carcinoma. Accordingly, risk factors for the development of cervical squamous cell carcinoma reflect increased likelihood of HPV exposure, such as age at first intercourse, early marriage, multiparity, and low socioeconomic level,[162–164] as well as cigarette smoking.

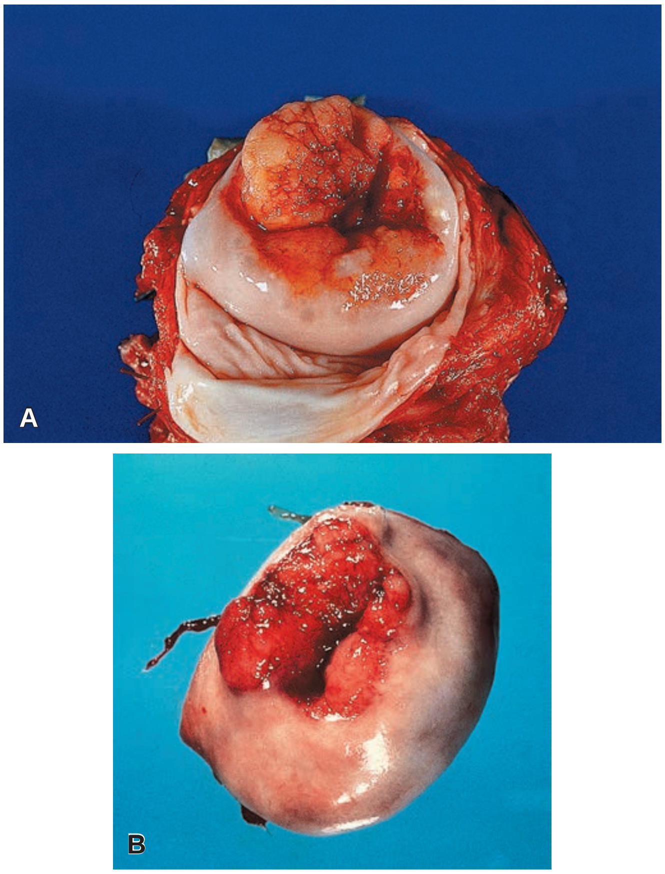

Figure 32.24 **A and B,** Gross appearance of invasive squamous cell carcinoma of cervix.

Host immune response factors contribute to the persistence of HPV infection and progression to HSIL (CIN2/3). Genes in the human leukocyte antigen (HLA) region of chromosome 6 are associated with increased susceptibility to the transforming properties of high-risk HPV. Impaired immune function, such as immunosuppressant therapy in organ transplantation recipients and HIV infection, is associated with a 5- to 10-fold increased risk of cervical neoplasia.[165]

Squamous cell carcinoma can be associated with microscopically similar tumors in the lower and upper genital tracts. In some of these cases, the same clonal pattern has been demonstrated, consistent with a cervical origin of the tumor followed by migration to other areas.[166] Despite this molecular evidence of clonality and therefore metastatic behavior, these metachronous tumors (that usually involve first cervix, and later vulva) behave like independent primary tumors.

Morphologic Features

Grossly, cervical carcinoma may be polypoid or deeply infiltrative (Fig. 32.24). The bulky carcinomas that grow out of the cervix are less likely to invade surrounding structures than are the infiltrating ones. The general truism that exophytic tumors are less aggressive than endophytic tumors thus holds true for cervical squamous cell carcinoma.

Some tumors are either clinically inapparent or simply missed by the examiner and are first discovered on pathologic examination

Table 32.1 Definitions of AJCC TNM for cervical carcinoma

Primary Tumor (T)

T CATEGORY	FIGO STAGE	T CRITERIA
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Cervical carcinoma confined to the uterus (extension to corpus should be disregarded)
T1a	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion of 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm, with a horizontal spread of 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2. Includes all macroscopically visible lesions, even those with superficial invasion.
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invading beyond the uterus but not to the pelvic wall or to lower third of the vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extending to the pelvic sidewall* and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involving the lower third of the vagina but not extending to the pelvic wall
T3b	IIIB	Tumor extending to the pelvic wall and/or causing hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4)

Regional Lymph Node (N)

N CATEGORY	FIGO STAGE	N CRITERIA
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1		Regional lymph node metastasis

Distant Metastasis (M)

M CATEGORY	FIGO STAGE	M CRITERIA
M0		No distant metastasis
M1	IVB	Distant metastasis (including peritoneal spread or involvement of the supraclavicular, mediastinal, or distant lymph nodes; lung; liver; or bone)

*The pelvic sidewall is defined as the muscle, fascia, neurovascular structures, and skeletal portions of the bony pelvis. On rectal examinations, there is no cancer-free space between the tumor and pelvic sidewall.

From Amin M, Edge S, Greene F, et al. (eds.). AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.

of a uterus removed for a benign condition.[167] Still others develop in the cervical stump left from a supracervical hysterectomy.[168]

Microscopically, three cellular variants of cervical squamous cell carcinoma exist, although admixtures and intermediate forms abound: *large cell nonkeratinizing*, *keratinizing* (Fig. 32.25), and *small cell*.[169–171] The latter should be distinguished from small cell neuroendocrine carcinoma, a tumor morphologically similar to small cell carcinoma of the lung and exhibiting features of neuroendocrine differentiation; immunohistochemistry may be necessary for this purpose. Although these patterns can be morphologically distinctive, they are not clinically relevant, in terms of planning treatment or prognosis.[172,173]

Some cervical squamous cell carcinomas have a distinctly papillary pattern of growth; these need to be distinguished from verrucous carcinoma.[174]

Other squamous cell carcinomas are accompanied by acantholysis, which may result in a pseudoglandular pattern.[175] Amyloid deposition

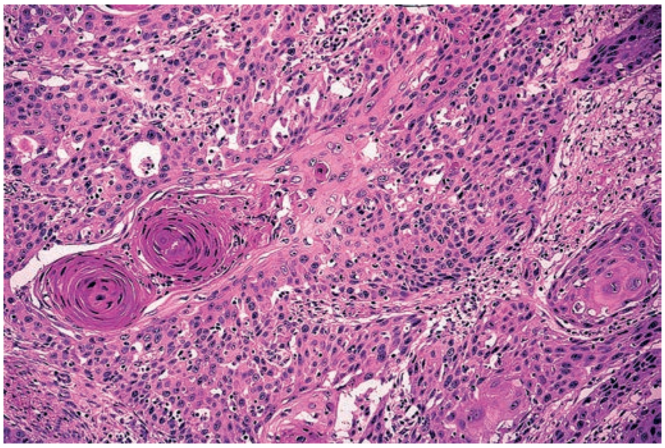

Figure 32.25 Microscopic appearance of invasive squamous cell carcinoma of cervix of large cell keratinizing type.

in the stroma has been documented in some other cases.[176,177] On occasion, cervical squamous cell carcinoma is found to be associated with intense infiltration by mature eosinophils, with or without accompanying peripheral blood eosinophilia; production of eosinotactic and eosinopoietic substances by the tumor cells has been suggested as the pathogenetic mechanism.[178,179]

Mucicarmine stains will demonstrate the presence of scattered droplets of cytoplasmic mucin in a minority of cases having the morphologic features of squamous cell carcinoma in routinely stained sections, a finding analogous to that sometimes encountered in carcinomas of the lung and other sites.[180] Their behavior seems to be the same as that of squamous cell carcinomas lacking mucin secretion.[180]

The exceptional occurrence of sebaceous differentiation in cervical carcinoma has also been documented.[181]

Immunohistochemical and Molecular Genetic Features

Immunohistochemically, squamous cell carcinomas of the cervix express keratins (nearly 100% of the cases), CEA (90%),[182] p63 (a homologue of p53 preferentially expressed in basal and immature cervical squamous epithelium),[183] and p40. The range of keratins found in the tumor varies somewhat depending on the subtype, but it is very wide.[184] There may also be reactivity for β-human chorionic gonadotrophin (β-hCG),[185] and for parathyroid hormone–related gene (although these tumors rarely give rise to hypercalcemia).[186]

In contrast to the situation in many other human malignancies, the *TP53* gene is rarely mutated in cervical squamous cell carcinoma; this is also true for the biologically related *MDM2* gene.[187] Despite the lack of mutation in *TP53*, the function of the gene is inactivated due to the effect of HPV-associated E6 protein, which binds to p53 protein, causing its rapid degradation.[165] The *RB* gene function is similarly inactivated due to binding of HPV-associated E7 protein with RB protein.[165]

Spread and Metastases

Cervical carcinoma spreads characteristically by direct extension to the vagina, corpus (endometrium and myometrial wall), parametrium, lower urinary tract, and uterosacral ligaments (Fig. 32.26).[188,189]

Lymph node metastases are also common. The pattern of involvement generally proceeds in a sequential fashion. The first station is represented by the paracervical, hypogastric, obturator, and external iliac groups and the second by the sacral, common iliac, aortic, and inguinal groups.[190] The incidence of nodal involvement is directly related to the stage of the disease. Hematogenous metastases were rare in older series, but with better control of the local lesion, they have increased in frequency.[189] Lung (9%) and bone (4%) are the most common sites.[191–193] Ovarian metastases are less common than with endometrial adenocarcinoma, but they do occur.[194]

The differential diagnosis between primary pulmonary squamous cell carcinoma and a pulmonary metastasis from a cervical carcinoma, which can be very difficult on morphologic grounds, is greatly aided by the detection of HPV in the latter by in situ hybridization, PCR, or immunostaining for p16.[195,196]

Treatment

Invasive carcinomas of the cervix that are more advanced than stage Ia1 can be treated with curative intent by surgery or irradiation with or without chemosensitization.[197–200] The choice depends on the extent of the tumor, the general condition of the patient, and the expertise available at the institution where the patient is treated. Early lesions can be treated just as effectively with hysterectomy or intracavitary radiation with platinum chemotherapy to radiosensitize the tumor cells[198,201,202]; for stage IIa lesions, irradiation alone and a combination of irradiation and surgery have yielded equivalent results in randomized studies.[203] As a rule, however, one is looking to use either surgery OR radiation therapy as the primary treatment modality, and not both, which results in the patient experiencing the morbidity and mortality of both procedures. Surgery is generally preferred for early carcinomas as the patients are typically young and surgery does not have the complication of late (>10 years) development of secondary malignancies in the radiated field. In some centers sentinel lymph node(s) are sent for frozen section at the start of the procedure, and if positive, radical hysterectomy is not performed since radiation therapy is indicated based on the positive node. If the sentinel node(s) frozen section is negative, surgery proceeds as planned, with the understanding that frozen section is not completely sensitive and that on permanent sections occasional micrometastases will be detected that were not present on frozen section examination.[204]

Early lesions can be treated conservatively with radical vaginal trachelectomy, a fertility-preserving procedure where the cervix is excised at the level of the upper endocervix or lower uterine segment along with a vaginal cuff and parametria, and pelvic lymph nodes.

In cases of central pelvic relapse of cervical carcinoma, pelvic exenteration should be seriously considered because a considerable number of the patients will have tumor confined to the pelvis.[205] This operation removes all pelvic viscera and lateral pelvic lymph node–bearing tissue. The bladder (anterior exenteration), rectum (posterior exenteration), or both may be removed, depending on the location of the tumor. At laparotomy, the surgeon should examine the upper abdomen carefully, particularly the periaortic area, for evidence of spread outside the pelvis. Any suspicious lymph nodes or liver nodules should be submitted to the pathologist for frozen section before the operative procedure is begun. Gross appraisal of enlarged extrapelvic nodes is unreliable, whereas frozen section examination is a highly accurate procedure.[206] The study of the surgical specimen should include a careful examination of the lymph nodes, the lateral edges of the resection, and the local extent of the tumor. Microscopically, the nodes, vessels, and adjacent organs should be examined for evidence of tumor. The finding of greatest prognostic relevance in the pathologic evaluation of pelvic exenteration specimens is the presence or absence of lymph node metastases.[207]

The microscopic examination of postradiochemotherapy specimens can be difficult due to the extent of regressive changes manifested in the tumor cells by cytoplasmic eosinophilia, vacuolization, and foamy degeneration. Prognostically, the most important feature to look for in these specimens is tumor embolism.[208]

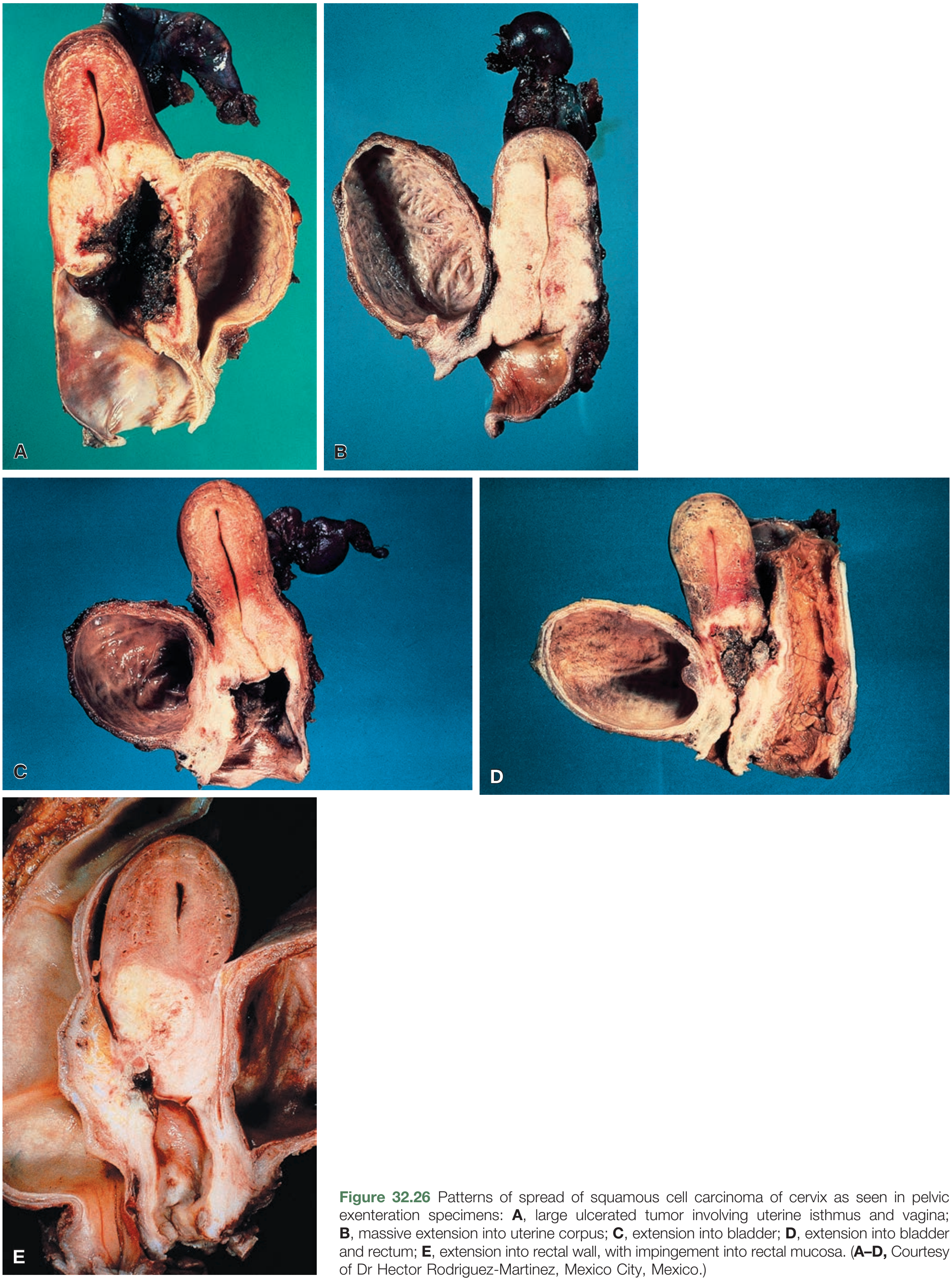

Figure 32.26 Patterns of spread of squamous cell carcinoma of cervix as seen in pelvic exenteration specimens: **A**, large ulcerated tumor involving uterine isthmus and vagina; **B**, massive extension into uterine corpus; **C**, extension into bladder; **D**, extension into bladder and rectum; **E**, extension into rectal wall, with impingement into rectal mucosa. (**A–D,** Courtesy of Dr Hector Rodriguez-Martinez, Mexico City, Mexico.)

Prognosis

The prognosis of cervical carcinoma is related to the following parameters:

1. *Clinical stage*. As for most other human malignancies, stage is the most important prognostic determinator.[209] It should be noted that clinical staging (FIGO) is used for cervical cancer, unlike for other organs. TNM staging is possible, but only for patients treated surgically; many patients are treated primarily by radiotherapy, and surgical pathology staging is not possible in these cases.
2. *Nodal status*. This is another crucial predictor, which is incorporated into the staging scheme.[210,211]
3. *Size* of the largest involved node[212] and *number* of positive nodes.[213]
4. *Size of the primary tumor*, as determined by measurement of the tumor's greatest diameter[214,215] or by volumetric techniques.[216]
5. *Depth of invasion*.[217–219]
6. *Endometrial extension*. The presence of this feature decreases the survival rate by 10%–20%.[220]
7. *Parametrial involvement*, as detected microscopically.[221]
8. *Blood vessel invasion*.[222–225]

Microscopic grade is not of prognostic significance, whether one uses the Reagan–Ng or the Broders method of grading.[225,226] This is in contrast to most other carcinomas. Our persistence in assigning a grade in pathology reports for cervical squamous cell carcinoma is a curiosity and will presumably stop in the near future, given that it is a useless practice. A similar comment applies to cell type (e.g., large cell nonkeratinizing) of squamous cell carcinoma; as noted previously, it is also not of prognostic significance.[172,173]

Other Microscopic Types

Verrucous carcinoma is a highly differentiated variant of squamous cell carcinoma with a polypoid pattern of growth, an extremely well-differentiated cytologic appearance, and a capacity for local invasion but not for metastatic spread. Some cases have been found to extend into the endometrial cavity.[227] Verrucous carcinoma should be distinguished both from condyloma acuminatum and from ordinary squamous cell carcinoma with a prominent papillary pattern of growth.[228,229] The general gross and microscopic features of this tumor are described in Chapter 30.

Spindle cell carcinoma (sarcomatoid carcinoma; squamous cell carcinoma with sarcoma-like stroma; carcinosarcoma) is morphologically analogous to the homonymous tumor in the upper aerodigestive tract.[230] It may contain osteoclast-like giant cells,[231] and there is often evidence of HPV infection.[232] The recognizable epithelial component of this tumor, when present, is of squamous type; this is in contrast with the malignant mixed müllerian tumor, in which that component is usually glandular. It is advisable to keep these tumors (both of which can occur in the cervix) in separate categories, although both of them probably represent carcinomas with a sarcoma-like component.

Basaloid (squamous cell) carcinoma is characterized by prominent peripheral palisading, an infiltrative growth pattern, and minimal stromal reaction (Fig. 32.27).[233] The behavior of this tumor is aggressive, as is also the case with the homonymous neoplasm in the upper aerodigestive tract. It is, therefore, very important to clearly separate this tumor from adenoid cystic carcinomas and adenoid basal carcinomas.[234]

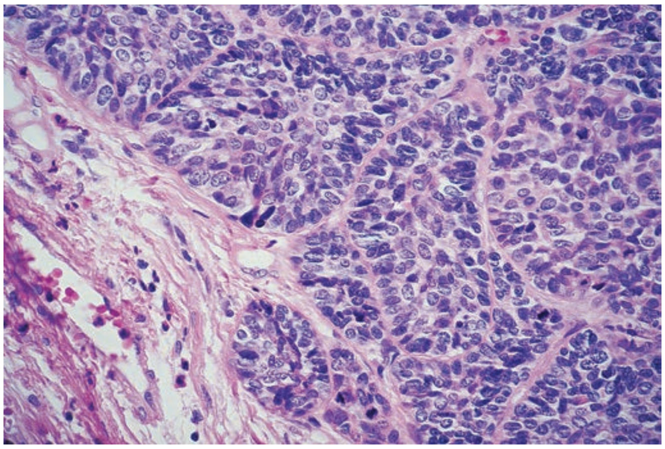

Figure 32.27 Basaloid Squamous Cell Carcinoma of Uterine Cervix. The tumor grows in the form of well-defined nests showing peripheral palisading.

Lymphoepithelioma-like carcinoma resembles its more common counterpart in the upper respiratory tract by virtue of the large size of the tumor cells, vesicular nuclei with prominent nucleoli, syncytial appearance, and heavy lymphocytic infiltration.[235–237] Some cases have been found to secrete β-hCG, as is also occasionally the case with conventional squamous cell carcinoma.[238] The possible association of this tumor with either EBV or HPV remains controversial.[239–241] This tumor type shows considerable overlap with the *circumscribed* type of cervical carcinoma that has been described.[242]

Adenocarcinoma

Background

Adenocarcinomas account for approximately 20% of all cervical cancers.[243,244] They appear to be relatively more common in those areas where cervical screening programs have reduced the incidence of invasive squamous cell carcinoma, as cervical screening is relatively less successful in detecting precursor lesions of adenocarcinoma.[245] Cervical adenocarcinomas have traditionally been subclassified based on tumor cell type, but this is slowly giving way to a classification mirroring that of vulvar squamous cell carcinoma (i.e., HPV associated versus HPV independent. The basis for this shift is the recognition that the morphologic features and prognosis are significantly different for tumors in these two major categories.[246–259] This is a recent development, and there remains much to be learned about the HPV-independent cervical adenocarcinomas in particular, but in recognition of this emergent trend the HPV-dependent and HPV-independent variants will be considered separately, later. As for other lower genital tract carcinomas, p16 immunostaining can serve as a surrogate test for HPV status, with "block positivity" indicating an HPV-associated tumor.[250–252] p16 immunostaining is not perfect, as p16 expression can be seen in any tumor with loss of p53 function and dysregulation of RB signaling, and has been described as an uncommon finding in HPV-independent cervical adenocarcinoma.[253] Conversely, p16 expression can be lost through mutation during progression of an HPV-associated tumor; therefore, when staining a large carcinoma one should preferentially select a block with adenocarcinoma in situ, which is almost invariably positive for p16 in HPV-associated cervical adenocarcinoma. In practice, if the morphologic features and p16 staining result are concordant, a tumor can be confidently classified as HPV associated or HPV independent. If there are discordant features, molecular testing for HPV nucleic acid can be used to determine HPV status, just as in vulvar squamous cell carcinomas.[247]

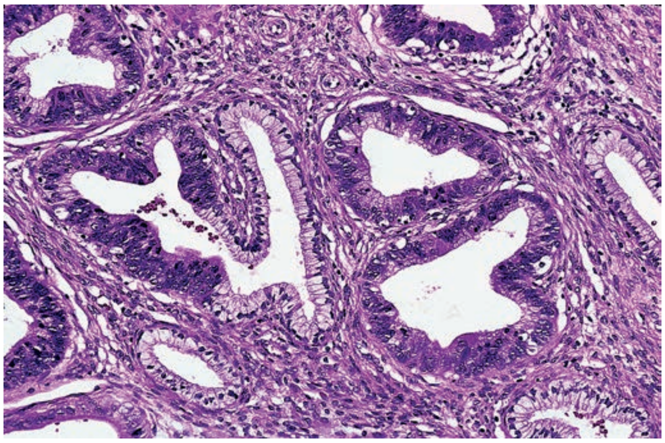

Figure 32.28 Adenocarcinoma in situ with partial preservation of endocervical glands.

In situ Adenocarcinoma

The documentation of the existence of an in situ stage of cervical adenocarcinoma lagged behind that of squamous cell carcinoma but is well established, at least for the HPV-associated cervical adenocarcinomas.[254,255] Cytologic atypia (manifested by nuclear hyperchromasia and pleomorphism) and increased mitotic figures are the two most important identifying features (Fig. 32.28). The presence of numerous apoptotic bodies is another diagnostic clue.[256] This combination of increased mitotic activity and numerous apoptotic bodies is characteristic of lesions induced by oncogenic HPV. The changes can be very subtle and limited to the endocervical surface.[257]

The mucins secreted by the in situ malignant glands may be similar to those of the normal endocervical mucosa or may resemble the pattern of intestinal goblet cells.[258] The latter, which is referred to as intestinal-type cervical adenocarcinoma in situ, shows consistent expression of CDX2.[259] Most in situ cervical adenocarcinomas are positive for CEA.[260] The cell proliferative index (as measured by Ki-67 immunostaining) is increased, there is an abnormal expression of cell cycle–related molecules, and the expression of hormone receptors is either decreased or absent.[261] Strong nuclear cytoplasmic positivity for p16, as a result of the association with HPV, is characteristic.[262] Glandular dysplasia short of that seen in carcinoma in situ has been described[263–268] but has not emerged as a well-defined diagnostic entity and is not a recommended category for routine diagnostic practice.

An important differential diagnosis of in situ cervical adenocarcinoma is with tubal or tubal–endometrial metaplasia.[269] The cells of tubal or tuboendometrial metaplasia can have increased N:C ratio but lack the stratification, nuclear atypia, numerous apoptotic bodies, or increased mitotic activity of adenocarcinoma in situ. Patchy p16 positivity may be seen in tubal or tuboendometrial metaplasia, but they lack the strong diffuse "block" positivity of adenocarcinoma in situ.

Almost half of the invasive HPV-associated cervical adenocarcinomas and approximately 75% of their in situ counterparts have an associated HSIL (CIN2/3) of the overlying epithelium.[270–272]

Stratified mucin-producing intraepithelial lesions (SMILEs) are uncommon intraepithelial lesions that may be seen in association with adenocarcinoma or adenosquamous carcinoma of the cervix.[273,274] More typical HSIL (CIN2/3) or adenocarcinoma in situ may also coexist. SMILE consists of stratified epithelial cells with nuclear atypia and a high proliferation index/strong diffuse p16 positivity that differs from HSIL in there being abundant intracellular mucin (Fig. 32.29). It is considered to be an uncommon variant of adenocarcinoma in situ or adenosquamous carcinoma in situ.[273]

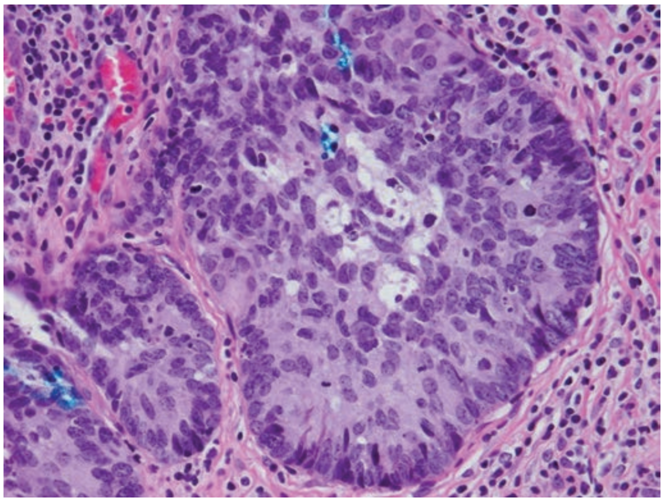

Figure 32.29 SMILE, a morphologically subtle variant of adenocarcinoma in situ/adenosquamous carcinoma in situ. (Courtesy of Dr Lien Hoang, Vancouver, Canada.)

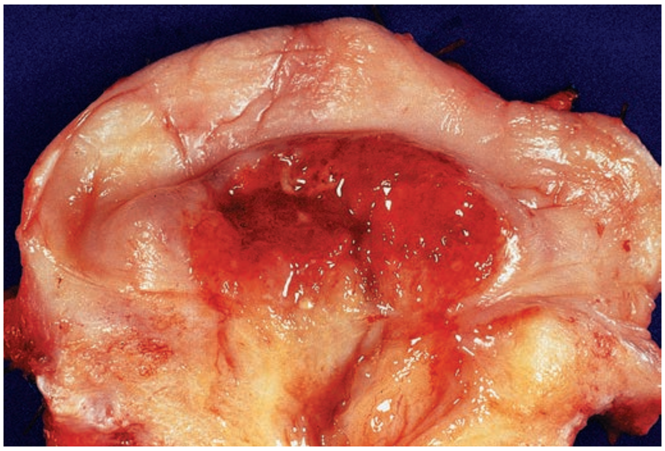

Figure 32.30 Gross appearance of endocervical adenocarcinoma.

Conization or LEEP is the treatment of choice for in situ adenocarcinoma of the cervix.[275] The circumferential extent of tumor is a marker of residual/recurrent disease, and it is therefore important to include this information in the pathology report.[276,277]

Human Papilloma Virus–Associated Cervical Adenocarcinoma

General Features

The HPV-associated tumors account for a large majority of cervical adenocarcinomas. These tumors present no distinguishing gross characteristics compared to their squamous cell counterparts (Fig. 32.30). Microscopically, the most common pattern is that of a well-differentiated glandular pattern with mucin secretion, some of which can leak into the stroma (Fig. 32.31).[278–282] However, the degree of differentiation varies, and poorly differentiated forms exist. Most HPV-associated cervical adenocarcinomas are of "usual type," as per the 2014 WHO classification of cervical adenocarcinomas, but other cell types can be seen and are described later. These morphologic variants may coexist in a given case, and there is considerable

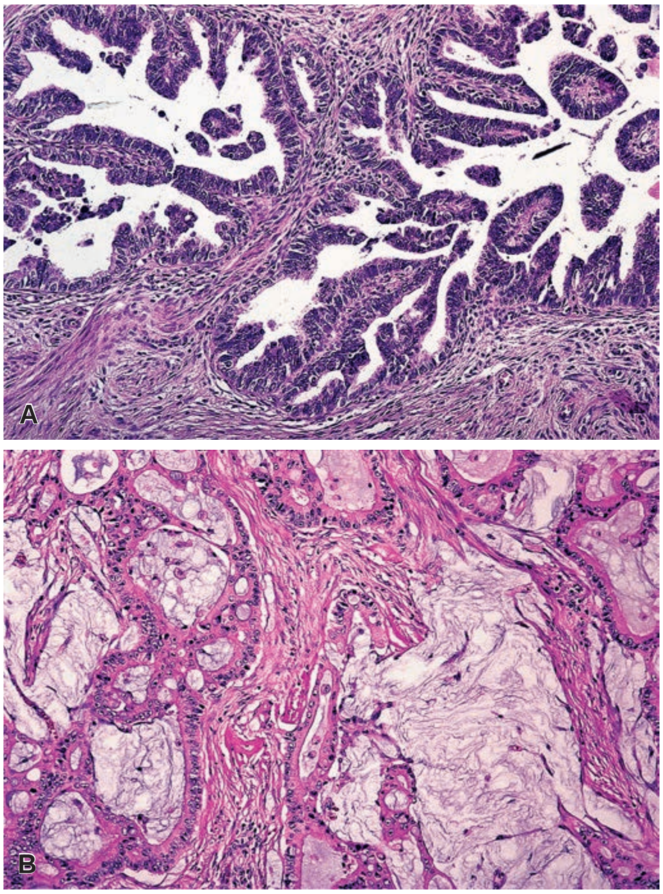

Figure 32.31 Microscopic appearance of HPV-associated adenocarcinoma of usual type. Note the variable amounts of mucin in **A** compared with **B**.

inter-observer variation in their application. Moreover, they are of doubtful significance as meaningful subcategories of HPV-associated cervical adenocarcinoma as they do not impact on patient management.

Histochemically, alcian blue– and mucicarmine-positive material is found intracellularly in nearly all cases of conventional cervical adenocarcinoma.[283] Among the mucins, there is positivity for MUC1 in nearly 100%, MUC2 in 40%, MUC4 in 75%, and MUC5AC "in most."[284] Keratins, EMA, and CEA are consistently expressed, whereas vimentin is not.[285–288] Estrogen and progesterone receptors are expressed in only one-fourth of the cases.[289] About one-fourth of endocervical adenocarcinomas are positive for CDX2, CK20, or both; this profile usually (but not always) correlates with intestinal differentiation.[290,291] It should be noted that intestinal differentiation, with goblet cells, can be encountered in HPV-associated tumors but is also commonly seen in HPV-independent tumors. Cervical adenocarcinomas have also been shown to contain argyrophilic (presumably neuroendocrine) cells,[292] a variety of peptide hormones,[293] and mammaglobin (although not as commonly as endometrial adenocarcinoma).[294]

A pattern-based classification of cervical adenocarcinoma that can be applied irrespective of histotype/HPV status has been proposed by Roma et al.[295] Invasive adenocarcinomas are subclassified as category A, B, or C. Category A is characterized by well-demarcated glands with rounded contours, with no destructive invasion (i.e., no single cell infiltration or lymphovascular invasion); this category includes tumors that would be considered to be entirely in situ by some observers. Category B shows limited destructive invasion, while category C shows diffuse destructive invasion. The most interesting finding is that none of the patients with A pattern invasion in their tumors had nodal metastasis.[295] In a follow-up study, it was demonstrated that the interobserver agreement in assignment of invasive category was superior to that of diagnosis of invasive versus noninvasive by typical criteria.[296] The main drawback to application of the classification is that, while the reproducibility is good ($\kappa = 0.65$), there are significant numbers of cases where pathologists cannot agree on the category,[296] making it difficult to make treatment decisions (i.e., whether to do radical surgery with lymph node dissection) based on this feature. An important practical point that has come out of this classification is confirmation that in those too frequent cases where the differential diagnosis rests between in situ adenocarcinoma and the subtle category A pattern of invasion, the distinction is not clinically important because both groups have an excellent prognosis with minimal chance of nodal metastasis. One final observation is that it in our experience category C pattern of invasion appears to be more commonly encountered in HPV-independent gastric-type adenocarcinomas; it will be interesting to see if this is a significant association and, if so, whether the pattern of invasion or HPV status is the more important prognostic indicator.

Cervical adenocarcinoma spreads directly to endometrium and vagina and metastasizes to the regional nodes, with a distribution pattern similar to that of cervical squamous cell carcinoma (see earlier). It can also metastasize to the ovaries, especially when extending to the lower uterine segment.[297,298] Those reported cases of combined endocervical adenocarcinoma and ovarian mucinous adenocarcinoma (and occasionally even tubal adenocarcinoma)[299,300] that were formerly considered to be independent primary tumors represent metastases of the cervical tumor to these organs.[297,298] p16 immunostaining or HPV testing of the ovarian tumor is useful in confirming the metastatic nature of these lesions.

The preferred therapies for cervical adenocarcinoma are surgery (especially for early lesions), chemo/radiation, or a combination of radiation and surgery.[301–303] The incidence of residual tumor in the hysterectomy specimens after intracavitary treatment is much higher than for squamous cell carcinoma.[304] The prognosis depends on the clinical stage, amount of tumor (as determined by tumor volume), microscopic grade, and nodal status.[305–310] In most series, the overall prognosis has been less favorable than for the squamous cell counterpart, but the more aggresive HPV-independent cervical adenocarcinomas have not been excluded from these analyses and it's possible that they acccount for the subtle differences seen between adenocarcinomas and squamous cell carcinomas.[307,311,312] There is not much difference among the various histologic subtypes of HPV-associated cervical adenocarcinoma.[313] The presence of nodal metastases is an ominous prognostic sign.[314]

Morphologic Variants of Human Papilloma Virus–Associated Cervical Adenocarcinoma

Most endocervical adenocarcinomas diagnosed as **endometrioid adenocarcinoma** of cervix in the past are better diagnosed as usual type (HPV-associated) adenocarcinoma as they show the high mitotic rate, numerous apoptotic bodies, and strong diffuse p16 positivity, as well as frequent admixture with more conventional appearing HPV-associated cervical adenocarcinoma. The differential diagnosis includes endometrioid adenocarcinoma of the endometrium, which can be accompanied by a very deceptive pattern of cervical spread,[315] which is discussed further later.

Serous (papillary) carcinoma is analogous in appearance to the homonymous uterine and ovarian neoplasm, including the common occurrence of psammoma bodies.[316,317] It may be seen in association with usual type endocervical adenocarcinoma.

Villoglandular (papillary) adenocarcinoma presents as an exophytic polypoid lesion with papillae lined by endocervical, endometrial, or intestinal-type epithelium showing only mild atypia (Fig. 32.31). The appearance of the superficial portion is similar to that of colorectal villous adenoma.[318] At the base they show Silva pattern A,[295] with smooth contoured glands, without infiltrative features, and these may be in situ lesions. Most cases are associated with adenocarcinoma in situ and/or HSIL (CIN2/3).[319,320] The prognosis is excellent[321] but only if strict architectural and cytologic criteria (exophytic growth, smooth border with underlying stroma, bland appearance of the nuclei) are applied.[322] This diagnosis should NOT be made based on a small biopsy as there may be conventional invasive cervical adenocarcinoma underlying and a diagnosis of "well-differentiated villoglandular adenocarcinoma" will suggest a very favorable prognosis that does not reflect the underlying infiltrative component.

Adenosquamous (mixed) carcinoma combines adenocarcinoma with a well-defined squamous component.[323] Adenosquamous carcinoma should be distinguished from squamous cell carcinoma without glandular formations but with histochemically demonstrable intracellular mucin.[324] When compared grade by grade and stage by stage with adenocarcinomas and squamous cell carcinomas, no prognostic differences are found.[325,326]

Glassy cell carcinoma has been described as a distinct type of poorly differentiated adenosquamous carcinoma.[327] It occurs in a younger age group (mean age, 41 years) than other cervical neoplasms and often has been associated with pregnancy. The tumor cells have a moderate amount of cytoplasm with a ground-glass or finely granular appearance, a prominent eosinophilic and PAS-positive cell membrane, and large nuclei with prominent nucleoli. Mitoses are numerous. A prominent inflammatory infiltrate, often rich in eosinophils, is regularly seen in the adjacent stroma, and this may be accompanied by peripheral blood eosinophilia.

In pure cases of glassy cell carcinoma, glandular or squamous differentiation is absent, although it can be consistently detected by ultrastructural examination.[328] Other cases show an admixture with mucin-producing adenocarcinoma and/or clear-cut squamous foci, raising the question whether it is justified to regard glassy cell carcinoma as a distinct entity.[329,330] It is likely that there is significant interobserver variation in use of this diagnosis. The prognosis is poor.[331,332]

Adenoid cystic carcinoma is a specific variant of cervical adenocarcinoma that tends to occur in elderly multigravid women of African descent[333] and is associated with a particularly poor prognosis.[334,335] The morphologic appearance is similar to that of the homonymous tumors of salivary glands. Like the former, it may be cribriform (the most common pattern) or grow in a predominantly solid fashion.[336] Adenoid cystic differentiation may be present admixed with other patterns of HPV-associated cervical adenocarcinoma.[337]

Adenoid basal carcinoma (tumor; epithelioma) should be distinguished both from adenoid cystic carcinoma and from basaloid (squamous cell) carcinoma. Although it shares many phenotypic features with adenoid cystic carcinoma,[338] it is a very low-grade lesion, in contrast with the two neoplasms with which it can be confused. It is usually discovered incidentally, it does not produce a mass lesion, and—when pure—it does not result in metastases.[339,340] The consistent presence of oncogenic HPV has been documented.[341] The lesion blends with the process that has been called *adenoid basal hyperplasia*. Brainard and Hart[339] have proposed grouping these two conditions under the term *adenoid basal epithelioma* to emphasize their indolent nature. Adenoid basal carcinoma can be associated with frankly invasive carcinoma, which can show a range of morphologic features (e.g., squamous cell, adenoid cystic, or small cell neuroendocrine carcinoma); the behavior in these cases reflects the aggressive component.[342]

Other variants of endocervical adenocarcinoma, all of them exceedingly rare, are a microcystic type,[343] a signet ring type,[344,345] a small intestinal (enteric) type,[346,347] and a type with choriocarcinomatous and hepatoid differentiation.[348] The HPV status of these rare cervical adenocarcinoma variants remains to be elucidated.

HPV-Independent Cervical Adenocarcinomas

General Features

Only approximately 10% of cervical adenocarcinomas (and thus 2% of cervical carcinomas overall) are HPV independent,[349,350] and this is not a homogeneous group of neoplasms, as noted in the discussion of the different variants below. What they do seem to have in common is that they are not as likely to be identified on cytology smears, are more likely to present at advanced stage, and are associated with a worse prognosis compared to HPV-associated carcinomas.[247–250,253] The difficulties in cytologic detection probably reflects both the bland cytologic features of many of these tumors, as well as their location being more often in the upper endocervical canal, while usual type HPV-associated adenocarcinomas are characteristically at the squamocolumnar junction (like their HPV-associated squamous counterparts). At this time our understanding of these rare tumors is incomplete, but with accurate histopathologic diagnosis we will rapidly learn more about them, and it can be hoped that this will lead to improved management/patient outcomes. Indeed, unless pathologists accurately recognize these tumors, there is unlikely to be progress as clinical research starts with diagnosis.

Morphologic Variants of Human Papilloma Virus–Independent Cervical Adenocarcinoma

Gastric-type adenocarcinoma is a subcategory under "Mucinous carcinoma" in the 2014 WHO classification, along with intestinal type and signet ring type. This is an unfortunate grouping, as it combines tumors of radically different pathogenesis (i.e., HPV-independent and HPV associated). Gastric-type adenocarcinoma of the endocervix remains an ill-defined concept, but it is starting to be more widely recognized and routinely diagnosed.[247–250,253] It is characterized by well-formed glands lined by cells with voluminous clear or eosinophilic cytoplasm and distinct cell borders (Fig. 32.32).[247,248] They lack the high mitotic rate and numerous

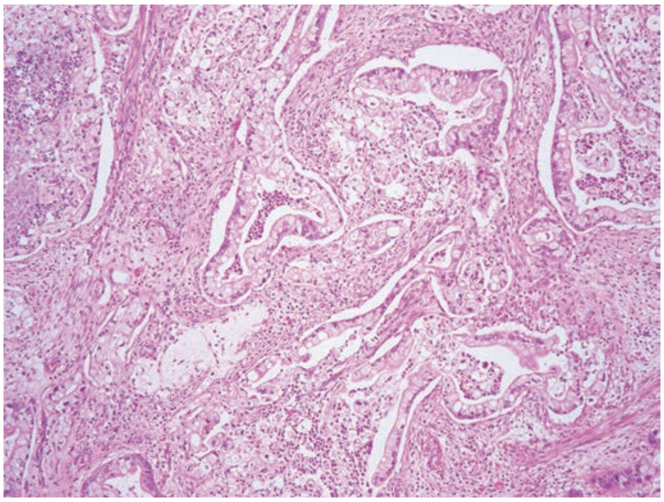

Figure 32.32 Gastric-type adenocarcinoma of cervix.

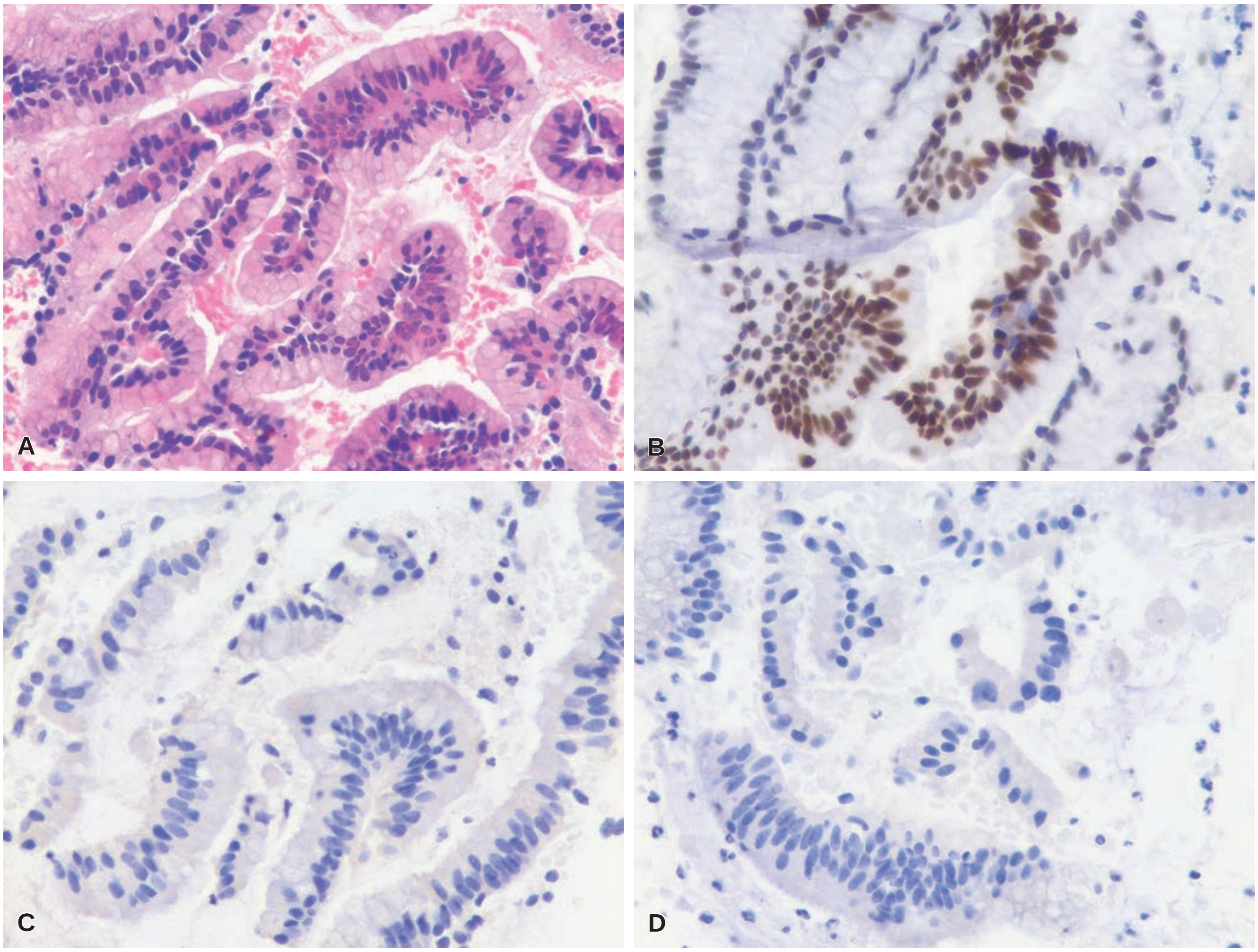

Figure 32.33 **A,** Endocervical curettings of a low-grade gastric-type adenocarcinoma of cervix. The cells show focal positivity for CDX2 **(B)** and are negative for ER **(C)** and p16 **(D)** expression.

apoptotic bodies of HPV-associated cervical adenocarcinoma. p16 immunostaining is helpful in distinguishing between gastric-type cervical adenocarcinoma and usual type HPV-associated adenocarcinoma, as the former typically shows no or only focal staining. There can be increased p16 immunostaining in a gastric-type adenocarcinoma that undergoes tumor progression to a higher-grade tumor (e.g., with *TP53* mutation), but this is uncommon.[253] CEA positivity can be used in the differential diagnosis with benign lesions such as microglandular hyperplasia that are CEA negative. The cells of gastric-type adenocarcinoma are usually completely negative for ER expression, an important consideration in distinguishing them from normal endocervical glandular epithelium or endometrioid carcinoma of endometrium; CDX2 expression is seen in approximately half of gastric-type adenocarcinomas (Fig. 32.33).[253] There can be considerable intratumoral variability in morphology, and although cells with abundant intracytoplasmic mucin are characteristic, there can be tumor progression and areas with less differentiated features and higher-grade nuclei. Goblet cells can be seen in approximately 25% of cases. At the advancing edge of the tumor, single cell invasion and/or signet ring cells may be identified. Most gastric-type adenocarcinomas are stage II–IV at presentation, in contrast to HPV-associated cervical adenocarcinoma where most are stage I.[249,254]

Adenoma malignum (minimal deviation adenocarcinoma) is a designation applied to particularly well-differentiated gastric-type cervical adenocarcinomas. It can be so well differentiated architecturally and cytologically that it can be diagnosed only as malignant because of the presence of distorted glands with irregular outlines deeply positioned in the cervix, and the fact that a portion of the infiltrating tumor is associated with a stromal response (Fig. 32.34).[351–354] Indeed, it is this very well-differentiated appearance that sets adenoma malignum apart from gastric-type adenocarcinoma, but it should be acknowledged that this distinction is artificial and adenoma malignum is best thought of as being within the category of gastric-type adenocarcinoma. It is not uncommon for a patient with adenoma malignum to have multiple superficial biopsies before a diagnosis of malignancy is made, because of the very bland cytologic features. About half of the cases have small foci with a less well-differentiated appearance; by definition this should comprise less than 10% of the tumor. Vascular and perineural invasion may be present. The fact that these tumors, like the more obvious adenocarcinomas, are CEA positive is of importance in the differential diagnosis with benign lesions such as microglandular hyperplasia.[355,356] HIK1083 has been introduced as a putative new marker for adenoma malignum, but this has not entered wide usage.[357] The differential diagnosis also includes endocervical-type *cervical adenomyoma*[358] and the condition known as *florid deep glands*,[359] in which atypia, architectural disarray, and desmoplastic stromal reaction are lacking. Curiously, **LEGH** is seen in association with 20% of adenoma malignum but less than 5% of non-adenoma malignum gastric-type adenocarcinoma.[247] Even though well differentiated, adenoma malignum is associated with advanced stage at presentation and poor prognosis, similar to that of less differentiated gastric-type adenocarcinomas.[247] Approximately one-third of gastric-like adenocarcinomas may be designated as adenoma malignum.[247] Some cases are associated with Peutz–Jeghers syndrome,[351,360] and mutations of the *STK11* gene (a tumor suppressor gene responsible for this syndrome and located at 19p13.3) have been found in over half of the cases of adenoma malignum.[361]

Clear cell carcinoma (formerly called *mesonephric carcinoma*) of the cervix is of müllerian rather than of mesonephric origin.[362] Glands lined by large cells with abundant clear cytoplasm are characteristic (Fig. 32.35). "Hobnail" cells are common, as are intraglandular papillary projections. Grossly, the tumor is usually exophytic. This tumor type is rare now, but there was a cluster of cases in young women associated with DES exposure in utero. At this time, most cases are encountered in older women.[363]

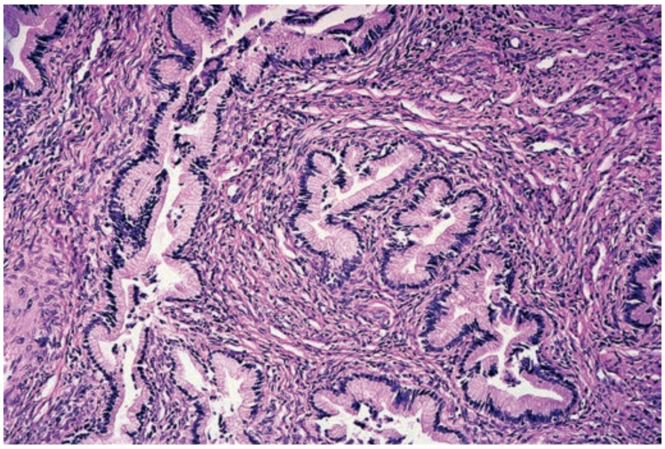

Figure 32.34 Adenoma malignum (minimal deviation adenocarcinoma), the very well-differentiated variant of gastric-type HPV-independent adenocarcinoma of cervix.

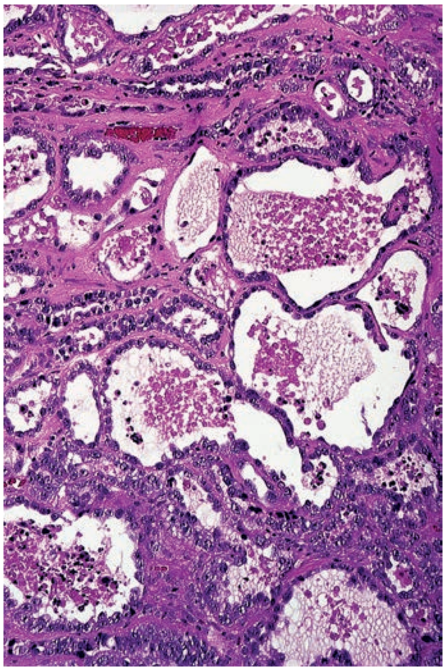

Figure 32.35 Clear cell adenocarcinoma of cervix showing tubular, microcystic, and tubulocystic features.

Mesonephric (adeno)carcinoma is a very rare tumor. Most of the cases that have been reported as such in the past probably represent müllerian-type adenocarcinomas or yolk sac tumors. True mesonephric carcinomas are often found adjacent to mesonephric hyperplasia (sometimes florid and atypical) and may exhibit a variety of patterns, such as ductal (resembling endometrioid adenocarcinoma), small tubular, retiform, solid, sex cord–like, and spindle (Fig. 32.36).[364–366] The immunohistochemical profile is similar to that of mesonephric rests and includes positivity for CD10, GATA3, and calretinin.[357] Tumors in which the epithelial component is admixed with either a homologous or a heterologous sarcoma-like component have been referred to as **malignant mixed mesonephric tumors**.[367]

Early Invasive Adenocarcinoma

Although early invasive adenocarcinoma is included in the College of American Pathologists checklist for reporting cervical adenocarcinoma, no definition is provided and it is preferable to simply measure depth of invasion and assign stage accordingly, exactly as described for squamous cell carcinoma of the cervix earlier in this chapter. That being said it must be acknowledged that it is considerably more difficult to both recognize and, when present, measure depth of invasive cervical adenocarcinoma.[296] Irregular nests of tumor cells and individual tumor cells are relatively uncommon, especially in HPV-associated cervical adenocarcinoma and adenoma malignum variant of HPV-independent adenocarcinoma. Invasion may only be recognized when glands with smooth contours are present in the outer half of the wall of the cervix (deeper than normal endocervical glands) or neoplastic glands are present in close proximity to thick-wall blood vessels (as defined by the distance from the closest gland to a thick-wall vessel being less or equal to the thickness of the vessel wall).[368] The prognosis for patients with equivocal or at most superficially invasive adenocarcinoma is favorable. For example, Ostor reported on 219 cases where there was invasion to a depth of 5 mm or less, and only 5 (2%) had nodal metastases.[369] Interestingly, 73 patients whose tumors showed Silva pattern A invasion (i.e., rounded glandular contour) were all alive and well on follow-up. These findings, from disparate studies, indicate that superficially

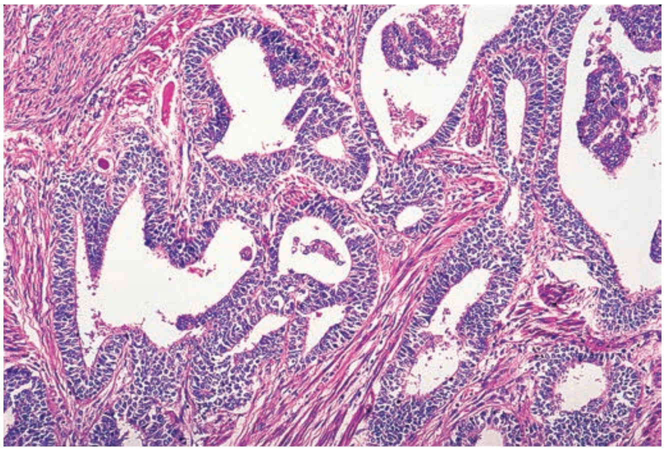

Figure 32.36 Mesonephric adenocarcinoma of cervix.

invasive cervical adenocarcinoma, especially if there is no destructive invasion, have a very favorable prognosis. In view of the generally indolent behavior of adenocarcinomas with equivocal or at most superficial invasion, a conservative type of surgery is advisable for most cases.[370]

Differential Diagnosis With Endometrial Adenocarcinoma

The differential diagnosis between endocervical and endometrial adenocarcinoma can be very difficult. The differential diagnosis is most commonly between usual type HPV-associated cervical adenocarcinoma and endometrial adenocarcinoma of endometrioid type, and it is this differential diagnosis that we will focus on. It should be noted that the guidelines do not apply if one is dealing with an HPV-independent cervical adenocarcinoma. We have encountered cases of gastric-type and mesonephric adenocarcinoma of the cervix where p16 negativity led to an erroneous diagnosis of endometrial carcinoma in a curetting specimen, so it is important to be mindful of the histologic features on H&E and not rush into immunostains.

Features that favor a primary endocervical origin are the following:

1. Presence of in situ adenocarcinoma in the cervical glands.
2. Negativity for vimentin.[371]
3. Negativity or only weak positivity for estrogen or progesterone receptor expression.[372,373]
4. Presence of HPV nucleic acid by in situ hybridization or PCR.[373]
5. Block positive immunoreactivity for p16.[374]

With regard to p16 immunostaining, it is important to note that up to 80% of the cells of some endometrioid carcinomas of endometrium can be p16 positive, but these tumors consistently lack the strong nuclear and cytoplasmic positivity characteristic of most HPV-associated endocervical adenocarcinomas of usual type. It is possible that a true endometrioid carcinoma could arise from cervical endometriosis; such a tumor would be HPV independent and immunophenotypically indistinguishable from endometrioid carcinoma arising in the uterine corpus or lower uterine segment; if these occur, they are rare. Tumors of the lower uterine segment are most commonly of endometrial-cell origin and indistinguishable from their counterparts arising in the uterine corpus rather than being related to endocervical adenocarcinomas.

Neuroendocrine Carcinoma

A small number of cervical carcinomas exhibit clear-cut evidence of neuroendocrine differentiation, as detected by ultrastructural, histochemical, and/or immunohistochemical criteria. These tumors have been variously called (atypical) carcinoid tumor, argyrophil cell carcinoma, (extrapulmonary) small cell carcinoma, (neuro) endocrine carcinoma, and carcinoma with (neuro)endocrine differentiation, the choice in terminology depending on the degree of differentiation of the tumor, the extent of endocrine features present, and the observer's bias.[375,376] It is preferable to use terms similar to those employed at other sites, as recommended in the 2014 WHO Classification, that is, low-grade neuroendocrine tumor (carcinoid or atypical carcinoid) or high-grade neuroendocrine carcinoma (small cell neuroendocrine carcinoma or large cell neuroendocrine carcinoma). It is important to remember that one can find neuroendocrine marker expression in cervical carcinomas of conventional type, a fact that should not result in a change of their designation; a diagnosis of neuroendocrine tumor can only be made in the presence of features of neuroendocrine differentiation recognizable on H&E.[377]

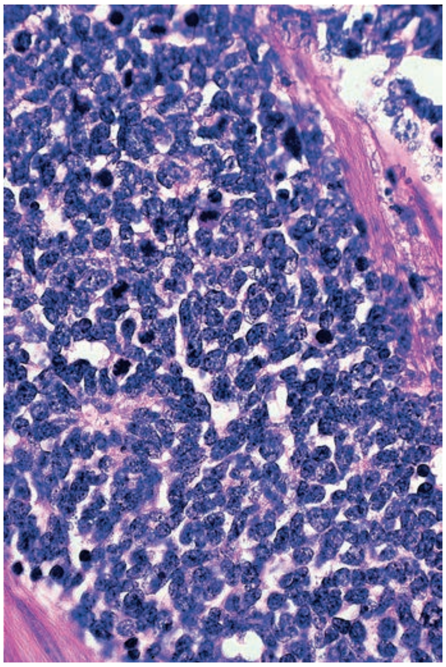

Figure 32.37 High-grade small cell neuroendocrine carcinoma of cervix.

Low-grade neuroendocrine tumors of the cervix are vanishingly rare, so we are left with small cell and large cell neuroendocrine carcinomas. The age distribution of patients with neuroendocrine carcinomas of the cervix is the same as for squamous cell carcinoma. They also show a similar association with HPV.[378–380] The carcinoid syndrome is invariably absent, but some cases have been seen in association with Cushing syndrome[381] and with inappropriate secretion of antidiuretic hormone (ADH).[382] In contrast to squamous cell carcinoma, HSIL (CIN2/3) changes in the adjacent epithelium are rare.[380,383] The histologic features of these tumors are identical to those of their more common counterparts occurring at other body sites. The large cell neuroendocrine carcinomas show variable organoid arrangement, with trabecular, insular, glandular, and spindle patterns of growth, while small cell neuroendocrine carcinomas are composed of monomorphic small cells with scant cytoplasm and hyperchromatic nuclei (Fig. 32.37). Most cases are pure, but others are combined with squamous cell carcinoma[384] or adenocarcinoma.[385–387] Immunohistochemically, positivity may be found for CD56,[388] chromogranin (but only in the better differentiated examples), and/or synaptophysin, but some tumors may be negative for all three markers. Generic neuroendocrine markers[389,390] and a variety of peptide hormones may be expressed (Fig. 32.38).[391] TTF-1 expression may be seen, so it does not aid in distinction from a lung primary.[392] p16 expression suggests HPV participation in the genesis of these tumors, which may be further confirmed at the molecular level.[393–396]

The large majority of these cervical neoplasms are histologically and clinically aggressive. The treatment, especially for high-grade lesions, usually consists of a combination of surgery, radiation therapy, and chemotherapy.[396] The prognosis is generally poor.[378,397–399] Naturally, there is also a close relationship between clinical stage and prognosis.[400] Both small cell and large cell neuroendocrine carcinomas with a polypoid shape or arising in polyps may be associated with a more favorable prognosis.[401]

Cytology

The broadest and most successful application of clinical cytology has been in the diagnosis of invasive carcinoma of the uterine cervix

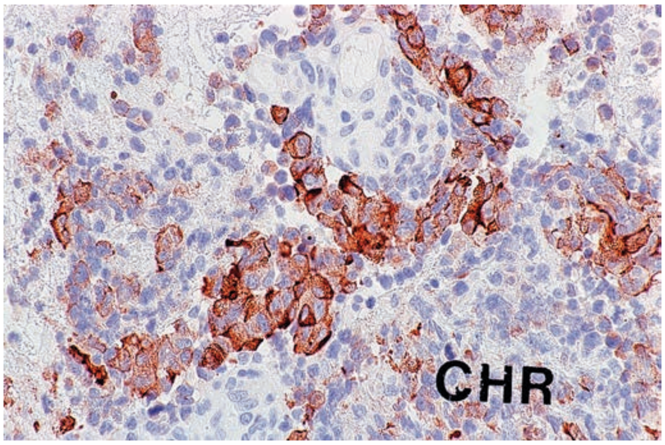

Figure 32.38 Strong focal immunoreactivity for chromogranin in neuroendocrine carcinoma of cervix.

and precursor lesions through the technique. Only a brief overview of cervical cytology can be provided in this chapter, and readers are referred to reference materials dedicated to cervical cytology, such as the excellent Bethesda 2014 website, for more detail on cytopathologic diagnosis of cervical smears.[402] There is a looming transition in which primary testing for HPV will have a place of more prominence, but there will also undoubtedly be large numbers of cervical cytology smears in need of skilled interpretation over the coming years, so that cervical cytology is undoubtedly going to be an important component of anatomic pathology practice. Cervical cytology was first described by Aureli Babès, a Romanian pathologist, further developed by George Papanicolaou at Cornell University, and is universally known as the Pap test[403,404] (Fig. 32.39). Today, it is widely used worldwide as a screening test in asymptomatic populations.[405,406]

Mass cytologic screening has shifted the presentation of cervical carcinoma from the clinical to the preclinical stage, saving many lives. In an often quoted article, Christopherson and Scott[407] reported a 70% decrease in mortality from carcinoma of the uterine cervix between 1970/1971 and 1955/1956 in women younger than 60 years of age. It should be emphasized that cervical cytology is a screening test, and the sensitivity is less than 100%. The success of cervical cancer screening programs in reducing mortality due to cervical cancer has led some to have unrealistic expectations for the performance of cervical smears in detection of premalignant and malignant lesions of the cervix.

Special techniques are applicable to cytology smears, including immunohistochemistry and in situ hybridization.[408] For instance, it has been shown that Ki-67 staining of cervical smears can improve the diagnostic accuracy of cervical LSIL,[409,410] while immunostaining for p16 is also of value in detection of HSIL.[411] The most important development, however, is development of sensitive automated HPV testing, with the previously described Hybrid Capture test being a leading example of the technology used. HPV testing was initially deployed as a triage test for patients with atypical cells that fell short of being diagnosable as SIL; results of HPV testing were used to guide referral for colposcopic examination in this setting. More recently there has been a move towards either co-testing (i.e., performing both conventional cervical smear cytologic examination and HPV testing) or primary HPV screening, where only HPV testing is performed as a screening test with no cervical smear cytology examination. The basis for the increasing use of HPV testing is that it is more sensitive than cervical cytology.[412–415] In the ATHENA study of more than 45,000 women, HPV testing had a sensitivity of 85%–90% in the four participating laboratories, while the sensitivity of cervical screening was both less, and showed more interlaboratory variation (42%–73%).[413–415] Given the added cost of co-testing, with little improvement in sensitivity, it is likely that there will be a move to primary HPV screening over the coming years. One such approach would stratify patients based on their HPV test results as follows: (1) women with negative tests will have no further testing done and return for HPV screening at regular intervals; (2) when testing is positive for HPV-16 or 18, there is reflex referral for colposcopic examination; and (3) with detection of other HPV genotypes, cervical cytology smears are prepared to guide referral to colposcopic examination (and if those smears are negative repeat testing is done in 12 months, which is at an accelerated interval). Primary HPV screening has already been instituted in some parts of the world (e.g., Mexico and Turkey).

The reader has undoubtedly noted that this is an area in transition. The uncertainty and change is also impacted by the emergence of patients at the age for initiation of screening (starting no earlier than at age 25) who were vaccinated against HPV as children or young adults. There are predictable effects of these highly effective vaccines on screening programs, in that there will be less HSIL in this population and this lower prevalence will lead to further decreases in both the sensitivity and specificity of cervical cytology screening, which is likely to disappear as a primary screening modality in immunized patients. HPV testing in this population will suffer from decreased specificity (although sensitivity should remain high) and more of the positive tests will be associated with transient infections that will be cleared by the immunized patients rather than progress to SIL. As well, there will be a higher proportion of non-HPV-16 and non-HPV-18 detected, and in these patients the risk of progression to HSIL is less.

The recommended terminology to be used in cervicovaginal cytology is that of the 2014 Bethesda classification.[428] There has been very significant evolution of diagnostic terminology within the memory of many senior practitioners, which we will briefly review. Papanicolaou's original system had five "classes" of increasing atypia. Although this nomenclature fulfilled a very important role in the establishment of the technique, it was eventually abandoned because of the vagueness of the information provided. A "class III" smear, for instance, could represent anything from a moderate dysplasia to an invasive carcinoma. Therefore, it was progressively replaced in the 1960s by the nomenclature then in vogue among histopathologists (i.e., negative, benign atypia, dysplasia [mild, moderate, or severe], carcinoma in situ, and invasive carcinoma).[416,417] During the 1970s, many institutions switched to the CIN system for both cytologic and histologic specimens. In 1988, at the initial Bethesda meeting, it was recommended to classify SIL in the following categories: (1) atypical squamous cells of undetermined significance (ASCUS); (2) low-grade SIL; (3) high-grade SIL; and (4) squamous cell carcinoma.[418–420] This classification was criticized on several grounds, one of them being the claim that it leads to overtreatment of many individuals whose smears are placed in the low-grade SIL category.[421,422] Partly as a response to these criticisms, the system was revised in 2001 in order to facilitate triage of women for more intensive screening only when a strong suspicion of a high-grade lesion is present.[423,424] The current classification (Bethesda 2014) includes the following categories for squamous cell abnormalities:

1. Atypical squamous cells:
   a. Of unknown significance (ASCUS)
   b. Cannot exclude high-grade squamous intraepithelial lesion (ASC-H)
2. Low-grade squamous intraepithelial lesion (LSIL)
3. High-grade squamous intraepithelial lesion (HSIL)
4. Squamous cell carcinoma

The recommendation is for women with ASCUS to be managed using a program of two repeat cytology tests, immediate colposcopy,

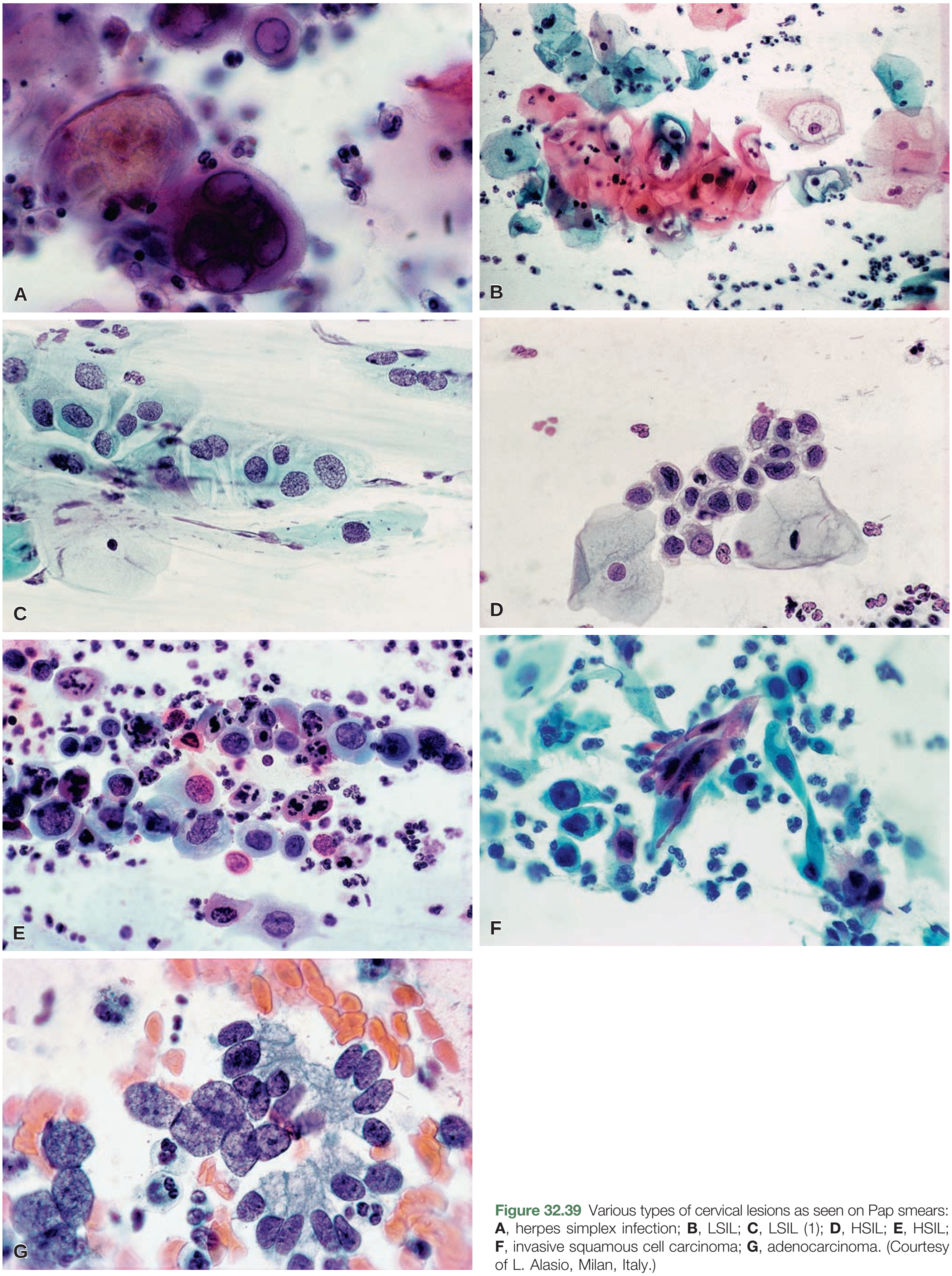

Figure 32.39 Various types of cervical lesions as seen on Pap smears: **A**, herpes simplex infection; **B**, LSIL; **C**, LSIL (1); **D**, HSIL; **E**, HSIL; **F**, invasive squamous cell carcinoma; **G**, adenocarcinoma. (Courtesy of L. Alasio, Milan, Italy.)

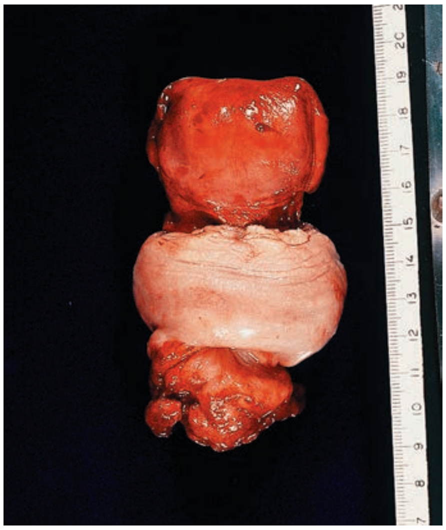

Figure 32.40 Embryonal (botryoid) rhabdomyosarcoma of cervix protruding in the form of grapelike masses.

or DNA testing for high-risk types of HPV, while patients with LSIL or HSIL are reflexly referred for colposcopic examinaiton.[425]

Whether there is co-testing or primary HPV screening, and even if the uptake of the vaccine is 100%, there will still be cervical cancer and cervical cancer deaths. There remain pockets of patient resistance to vaccination, based on pseudoscience and despite demonstration that HPV is so ubiquitous that 80% of sexually active women will be exposed by age 50. Furthermore, not all cervical cancers are related to HPV; in the previous section we discussed the HPV-independent cervical adenocarcinomas (e.g., gastric type or clear cell carcinomas) and these will not be detected by HPV testing and are suboptimally detected by cervical screening.

Other Tumors and Tumorlike Conditions

Carcinomas of one type or another comprise approximately 99% of all primary cervical malignancies. The remaining 1% is made up of a large variety of neoplasms.

Embryonal (botryoid) rhabdomyosarcoma presents in children and adolescents as a myxoid polypoid mass covered by attenuated epithelium.[426–428] The appearance is generally similar to that of the homonymous vaginal tumor. However, some of the cervical cases occurring in older patients have been seen to contain cartilage and to be associated with a better prognosis, (Fig. 32.40).[429] **Alveolar rhabdomyosarcoma** has also been reported.[430]

Carcinosarcomas (malignant mixed müllerian tumors) also present as polypoid masses but generally occur in much older patients, the average age in one series being 65 years.[431] Some tumors look identical to their more common uterine counterparts, but in others the recognizable epithelial component has an adenoid basal or squamous appearance.[431,432] When the latter is the case, the appearance blends with that of spindle cell (sarcomatoid) carcinoma.

Müllerian adenosarcoma[433,434] and **stromal sarcoma** of endometrial type also occur in the cervix (Fig. 32.41), the former sometimes featuring foci of ovarian sex cord–like structures.[435] **Smooth muscle tumors**, both benign and malignant, also occur in the cervix (Fig. 32.42).[436] The diagnostic criteria are the same as for those in the uterine corpus, but the ratio may be slightly different (comparatively more leiomyosarcomas are found in the cervix). Some of the reported leiomyosarcomas have been of the myxoid variety,[437] and others have had a xanthomatous appearance.[438]

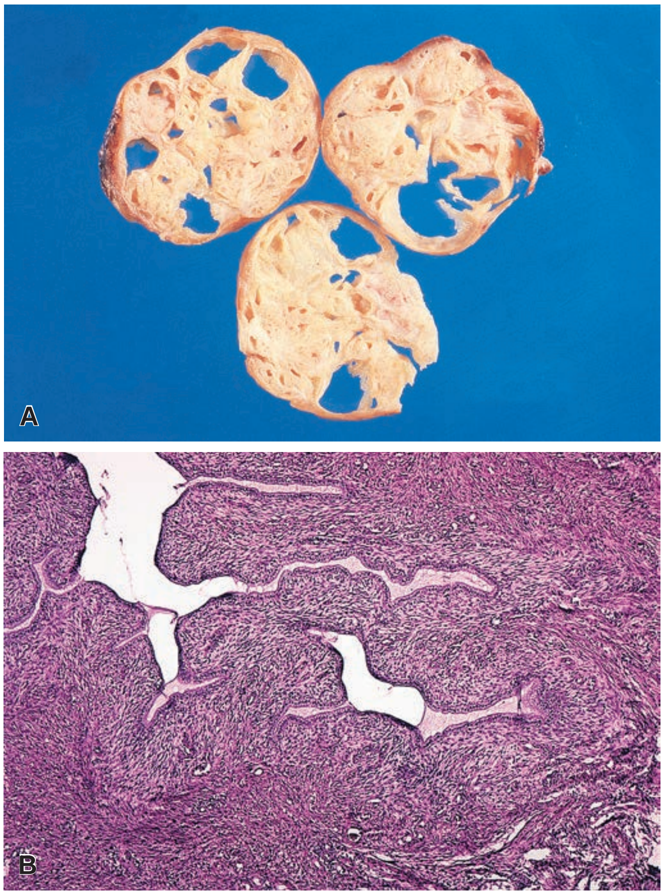

Figure 32.41 **A** and **B**, Müllerian adenosarcoma of cervix. **A**, Gross appearance. **B**, Microscopic appearance of typical adenosarcoma, with an appearance reminiscent of phylloides tumor of breast. (**A**, Courtesy of Dr Juan José Segura, San José, Costa Rica.)

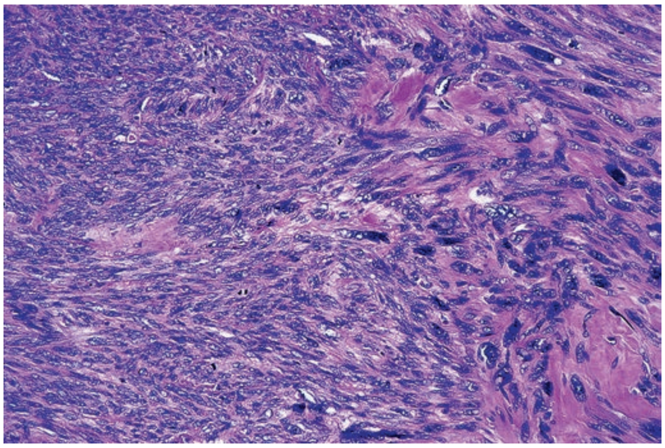

Figure 32.42 Poorly differentiated leiomyosarcoma of cervix.

Other primary cervical tumors and tumorlike conditions include *teratoma*,[439,440] *glial polyp (glial heterotopia, glioma)* of probable fetal origin,[441] and *ganglioneuroma*[442]; *yolk sac (endodermal sinus) tumor* (closely simulating the clinical appearance of embryonal rhabdomyosarcoma)[443]; *choriocarcinoma*[444]; *sebaceous carcinoma*[445]; *extrarenal Wilms tumor*[446]; *traumatic (amputation) neuroma*[447] (some occurring postpartum)[448]; *neurofibroma*[449]; *schwannoma*[450] (including the pigmented variety)[451]; *malignant peripheral nerve sheath tumor*[452,453]; *solitary*

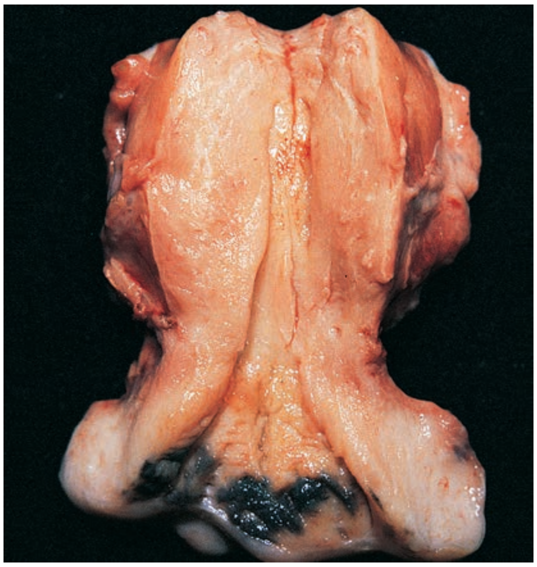

Figure 32.43 Gross appearance of blue nevus of cervix. (Courtesy of Dr Luis Spitale, Córdoba, Argentina.)

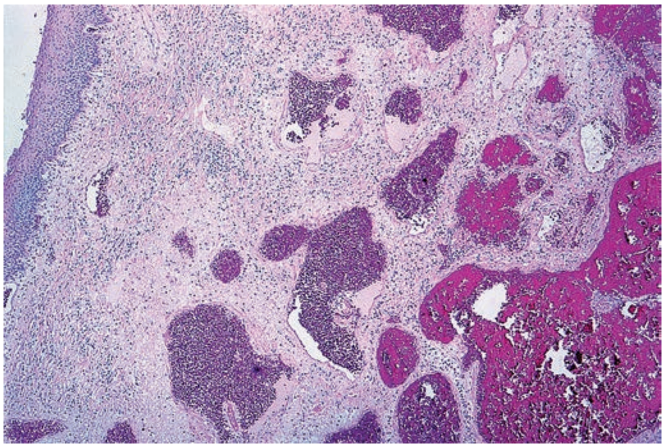

Figure 32.44 Cavernous hemangioma of cervix, a most unusual occurrence.

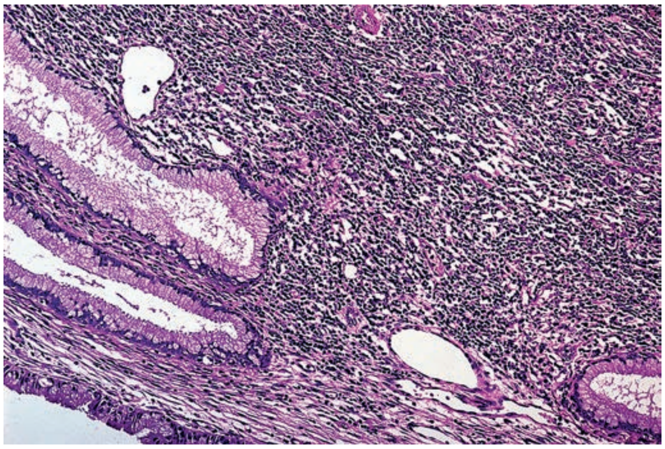

Figure 32.45 Diffuse large B-cell lymphoma of cervix growing between normal endocervical glands.

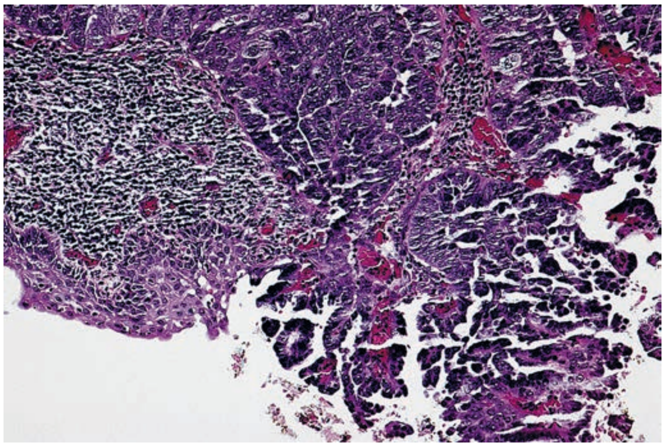

Figure 32.46 High-grade serous carcinoma of ovary metastatic to cervix.

fibrous tumor[454]; *pigmented neuroectodermal tumor of infancy*[455]; *melanosis* (sometimes developing after cryotherapy for SIL)[456–458]; *blue nevus*[459–461] (Fig. 32.43); *cellular blue nevus; malignant melanoma*[462,463] (including the desmoplastic variety[464] and a type simulating malignant peripheral nerve sheath tumor[465]); *benign mesenchymoma*[466]; *hemangioma*[467] (Fig. 32.44); *glomus tumor*[468]; *angiosarcoma*[469]; *osteosarcoma*[470]; *alveolar soft part sarcoma*[471–473]; and *Ewing sarcoma/PNET*[474–476]).

Malignant lymphomas of the cervix present with vaginal bleeding and a subepithelial mass without obvious ulceration.[477] Most are diffuse large B-cell lymphomas and many are accompanied by extensive fibrosis (Fig. 32.45).[475,478–481] An important differential diagnosis is with **lymphoma-like lesions** resulting from focally florid lymphoid proliferation associated with chronic cervicitis or as an expression of infectious mononucleosis[482,483]; these are identified by the polymorphic nature of the infiltrate (including mature plasma cells, small lymphocytes, and neutrophils), surface ulceration, and minimal or no sclerosis. Despite the occasional detection of clonality in some cases, the disease has so far followed a benign clinical course.[484] *Granulocytic sarcoma (chloroma)*,[485–487] *Hodgkin lymphoma, inflammatory pseudotumor*,[488] localized *amyloidosis*,[457] and *Rosai–Dorfman disease* (sinus histiocytosis with massive lymphadenopathy)[489] can also present initially as a cervical mass.

Metastatic carcinomas to the cervix (excluding direct invasion from endometrial carcinoma) can originate from genital or extragenital organs; the most common sites are the ovary, large bowel, stomach, breast, and kidney (Fig. 32.46).[490,491] Some of them clinically and pathologically simulate the appearance of primary cervical carcinoma, including invasive and in situ cervical adenocarcinoma.[492] Knowledge of the clinical findings may make this mistake avoidable.

An exceptional event is represented by replacement of the endocervical (and endometrial) mucosa by metastatic mucinous tumor of the appendix.[479]

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33

Uterus: Corpus

Blake Gilks

CHAPTER CONTENTS

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Normal Anatomy

The adult nulliparous uterus is a hollow, pear-shaped organ that weighs 40–80 g and measures 7–8 cm along its longest axis. It is divided into the *cervix* (discussed in Chapter 32) and the *corpus*. The portion of the corpus cephalad to a line connecting the insertion of the fallopian tubes is the *fundus*. The two lateral regions of the fundus associated with the intramural portion of the fallopian tubes are referred to as the *cornua*. The portion of the corpus that connects with the cervix is called the *isthmus* or *lower uterine segment*.

The uterine cavity has a triangular shape and a length of approximately 6 cm. It is lined by the endometrial mucosa, which constitutes the inner layer (endometrium) of the organ. It is surrounded by a thick muscular layer (myometrium) and a serosal covering, the latter extending to the point of peritoneal reflection. Two useful clues to distinguish the anterior from the posterior side of a hysterectomy specimen at time of gross examination are: (1) the fact that the point of peritoneal reflection is *lower* on the posterior side; and (2) the fact that the uterine insertion of the fallopian tube is *posterior* to the insertion of the round ligament.[1]

The uterine lymph vessels drain to a rich network of lymph nodes, the main groups being parametrial and paracervical; internal (hypogastric), external, and common iliac; periaortic; and inguinal.

The endometrial mucosa is made up of glands and stroma. It is divided into a deeply seated *basal* layer and a superficial *functional* layer. The basal layer is the equivalent of the reserve cell layer of other epithelia and is responsible for the regeneration of the endometrium following menstruation. It is made up of weakly proliferative glands and spindled stroma. The functional layer is subdivided into two strata, the *compactum* (toward the surface) and the *spongiosum* (close to the basalis). The stroma is mainly composed of endometrial stromal cells (whose appearance changes considerably during the menstrual cycle, see later section) and vessels (of which the spiral arterioles are the most distinctive). Also present are stromal granulocytes. The immunohistochemical profile of endometrial stromal cells is "CD10 dominant" in relation to CD34, whereas the reverse is true for the endocervical stroma.[2] The phenotypic profile of the endometrial glands will be discussed in connection with the various pathologic conditions that affect that tissue[3,4]; suffice to warn the reader that two markers associated with breast and lung/thyroid—that is, mammaglobin and thyroid transcription factor-1 (TTF-1), respectively—can be expressed by endometrial cells.[5,6]

During childbearing age, the normal endometrium undergoes a series of sequential changes in the course of the ovulatory cycle that prepare it to receive the ovum (Fig. 33.1).[7] If the ovum is not fertilized, the proliferative endometrium is cast off by menstruation, and the cycle repeats itself. A normal endometrial cycle is associated with changes in both endometrial glands and stroma that allow the pathologist to diagnose microscopically the phase of the menstrual cycle.[8] In a series of classic articles, Noyes and colleagues.[9,10] set forth specific criteria by which a relatively accurate dating of the endometrium was made possible (Fig. 33.2). At one time it was common for pathologists to be asked to "date" endometrial biopsy specimens (i.e. assess the development of the endometrial glands and stroma, relative to the time of ovulation) that were taken for investigation of infertility, but such requests have dramatically decreased over the

Abstract

Endometrial biopsy and curetting specimens are among the most commonly encountered in general surgical pathology practice and can show a wide range of pathologic alterations. Many relate to perturbations in the normal hormonal environment, secondary exogenous hormones or shifts in endogenous hormone levels, for example, during the perimenopausal period. Endometrial carcinoma is the most common malignancy of the female reproductive organs and recent insights into the genomic subtypes of endometrial cancer have changed our understanding of the pathogenesis of endometrial carcinoma. As well as carcinomas, a range of sarcomas and biphasic tumors, such as adenosarcoma, also occur in the uterine corpus, and these are reviewed.

Keywords

Endometrium
hyperplasia
carcinoma
leiomyosarcoma
endometrial stromal sarcoma
The cancer genome atlas

past decade; nevertheless all surgical pathologists should be familiar with the normal cyclical changes in the endometrium.

In general, the changes are quite uniform throughout the functional endometrium.[9] The surface epithelium is less responsive to the hormonal influences than the glandular epithelium. For subnuclear vacuolation to be regarded as evidence of ovulation, it should be present in at least 50% of the functional glands present in the section, as patchy development of subnuclear vacuoles is a common finding in endometrium subject to prolonged unopposed estrogenic stimulation (so-called disordered proliferative endometrium). Neutrophils, which are seen in large numbers in areas of tissue degradation (beginning on day 26) are very rare during the other days of the cycle; they should be distinguished from the already mentioned stromal granulocytes, which do not stain for chloroacetate esterase.[11]

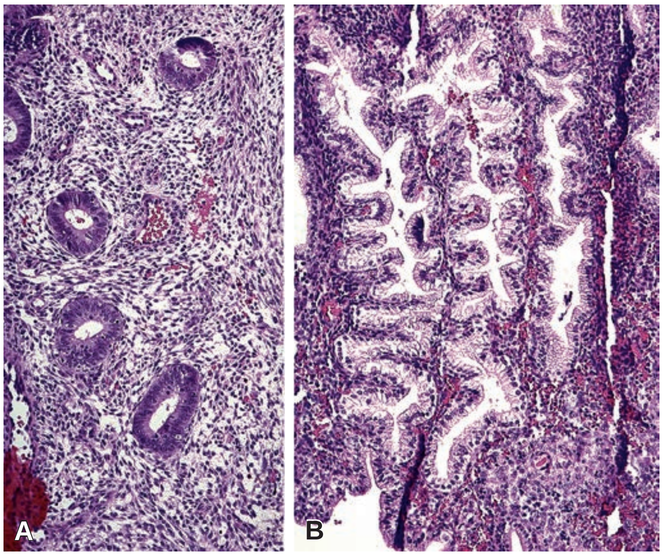


Figure 33.1 Normal Endometrium. A, Proliferative; **B,** secretory.

The cellular condensation with nuclear crowding, squamoid appearance, and focal cytoplasmic eosinophilia seen in menstrual specimens should not be confused with a malignant or other pathologic process. The possibility of overdiagnosis is even greater in the rare instances in which the menstrual endometrium is seen within the lumen of blood vessels.[12] It should be noted that endometrial tissue can also be found in myometrial vessels independently from menstruation.[13]

The basal layer of the endometrium is not subject to the influence of progesterone. Similarly, the mucosa of the lower uterine segment responds only sluggishly to the hormonal stimulation and can appear different from sampled functionalis.[14] This mucosa gradually merges with that of the endocervix; the hybrid endometrial–endocervical appearance of both glands and stroma allows its recognition in endometrial sampling (either biopsy or dilation and curettage [D&C] specimens).

The reappearance of glandular secretion and stromal edema once predecidual reaction is established—leading to the simultaneous presence of these three features in an endometrial specimen—is evidence that a fertilized ovum has implanted. An exaggerated expression of this pregnancy-related phenomenon is the ***Arias-Stella reaction***, as originally described by the Peruvian pathologist Javier Arias-Stella.[15] In this condition, secretory or proliferative changes in the endometrial glands are accompanied by prominent nuclear changes, manifested by hyperchromasia and marked enlargement (Fig. 33.3). Normal and abnormal mitoses may also be present.[16] These changes are almost always focal and may also occur in the cervix, endocervical polyps, adenomyosis, and endometriosis.[17] They are more often seen in postabortion curettings (present in 20%–70% of cases and persisting for weeks), but they are also seen in normal orthotopic or ectopic pregnancies, hydatidiform mole, choriocarcinoma, and (very rarely) following the administration of exogenous hormones.[18,20] In hydatidiform mole and choriocarcinoma, the nuclei of the endometrial cells may attain gigantic sizes. The most important

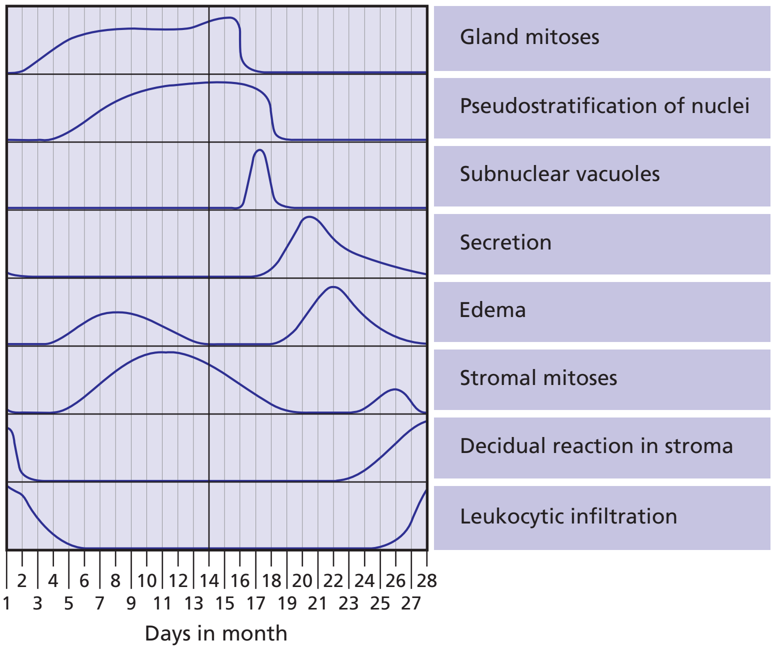


Figure 33.2 Cyclic Changes in Endometrium. Approximate relationship of microscopic changes. (From American Society for Reproductive Medicine. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. *Fertil Steril*. 1950;1:3–25).

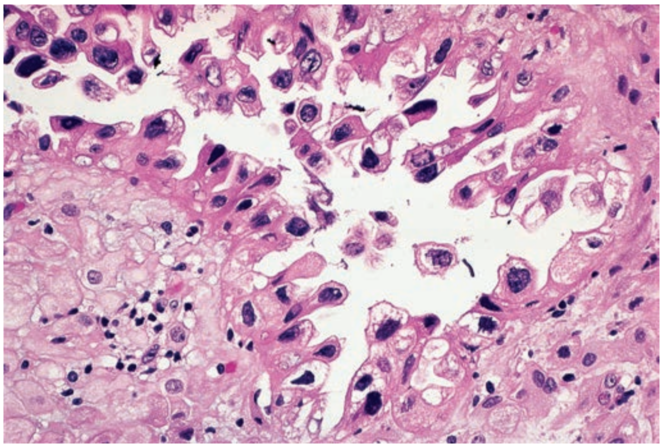


Figure 33.3 **Arias-Stella Reaction in Endometrial Mucosa.** This is not to be confused with a malignant condition.

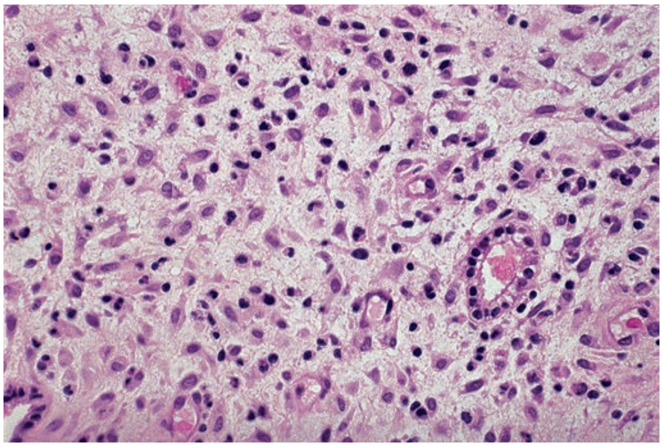


Figure 33.4 Typical appearance of endometrium after long-term administration of contraceptive pills. The glands are sparse and atrophic, whereas the stroma is prominent and has deciduoid features, reflecting the predominant progestin effect.

differential diagnosis is with serous and clear cell types of endometrial adenocarcinoma. Immunostains for Ki-67 and p53 are helpful in this regard, their being usually low and wild type–pattern, respectively, in the Arias-Stella reaction.[21]

Another interesting pregnancy-related endometrial alteration (often associated with the Arias-Stella reaction) is the focal appearance of optically clear nuclei in the glandular cells, simulating viral inclusions; these are due to the replacement of normal chromatin by a fine filamentous network that is immunoreactive for biotin.[22–24]

Exceptionally, an "idiopathic" decidual reaction is seen in the postmenopausal endometrium in the absence of an exogenous or endogenous source of progesterone excess.[25]

After the menopause the endometrium becomes inactive (simple glands lined by metabolically inactive, non-mitotic cuboidal epithelial cells and associated stroma) or atrophic (strips of inactive surface epithelial cells with no or minimal stroma). These glands may become cystically dilated (cystic atrophy), but the lining cells have an atrophic appearance, in contrast to the proliferative columnar cells lining cystic glands in endometrial hyperplasia without atypia. Although a distinction can be made between inactive and atrophic endometrium histologically, based on the presence or absence of endometrial stroma, it is not clinically relevant. Endometrial biopsy for postmenopausal bleeding is one of the most common specimens encountered in practice, with most such specimens showing the expected inactive/atrophic endometrium. In most series, approximately 5%–15% of the cases of postmenopausal bleeding are due to endometrial carcinoma and a similar proportion to endometrial polyps.[26,27] Degenerative and other changes in the endometrial blood vessels have been suggested as a possible etiology in the majority of cases where no significant pathology is identified (i.e. there is only the expected inactive/atrophic endometrium).[28,29]

The myometrium has a rich network of thick-walled vessels in its midportion, a landmark that can be recognized grossly. A peculiar vascular architecture sometimes encountered in the myometrium is that of arteries apparently free-floating within cleft-like spaces, which have been interpreted as venous channels.[30]

Effects of Hormone Administration

Estrogen Therapy

Exogenous administration of estrogen preparations exposes the cycling or postmenopausal endometrium to a potent stimulus.[31] Endometrial hyperplasia is a frequent development in women taking unopposed estrogen, and this can progress to atypical hyperplasia and adenocarcinoma.[32,33] The large majority of tumors arising secondary to unopposed estrogen are well differentiated and superficial and are associated with an excellent prognosis.[34]

Progestational Agents

Owing to the widespread use of progestational agents for therapeutic and contraceptive purposes, endometrial changes secondary to progestational effects are commonly encountered in practice.[35–37] The effects of exogenous progestins are seen primarily in the stroma, which predominates and shows striking pseudodecidual changes (Fig. 33.4).[38] In contrast to the prominent stromal development, the glands are small, widely separated by stroma, and atrophic appearing.

In endometrium from patients taking oral contraceptive pills, the effects in the endometrium reflect the progesterone predominance and variably show the features described previously, that is, stromal predominance, with pseudodecidual changes, and small atrophic glands.[39] On very rare occasions, focal glandular changes of the Arias-Stella type may appear in patients taking contraceptive pills. In most cases, discontinuation of the hormones results in a restoration of a normal endometrial pattern in a matter of weeks.

Patients receiving hormone replacement therapy for postmenopausal symptoms will typically be on low-dose combination (estrogen and progestin) therapy; the goal is to relieve symptoms but to not have stimulation of the endometrium. Thus, the endometrium should appear inactive or atrophic. If a patient on postmenopausal hormone replacement therapy presents with bleeding and the biopsy shows proliferative changes, this reflects excessive estrogenic stimulation of the endometrium; if the dosage is not altered, continued bleeding is likely.

Endometrial changes secondary to treatment of endometrial hyperplasia with high-dose progestin therapy will be covered later, in the section on endometrial hyperplasia.

The **Mirena coil (levonorgestrel)**, increasingly used for the treatment of menorrhagia/endometrial hyperplasia, can induce a large variety of alterations in the endometrial mucosa, including pseudodecidualization, mucinous changes, ulceration, inflammatory infiltrates, stromal hyaline nodules, superficial micropapillary changes, infarcted decidua, dystrophic calcification, and others.[40]

Progesterone receptor modulators used in the management of endometriosis and uterine leiomyomas most commonly cause only minimal and inconsistent changes in the endometrial mucosa but can cause cystic dilated glands that raise the differential diagnosis of endometrial hyperplasia.[41] These changes can be distinguished from hyperplasia by the appearance of the epithelial cells lining the cysts, which appear inactive and may contain abortive subnuclear vacuoles.[42] Abnormal stromal vessels are commonly seen.

Tamoxifen

Tamoxifen is a synthetic anti-estrogen used in the treatment and prophylaxis of breast carcinoma. Not only does it have an anti-estrogenic effect on the endometrium when competing with ovarian estrogen secretion, it also has a paradoxical estrogenic effect in the absence of ovarian estrogen secretion.[43–45] It is associated with an increased frequency of proliferative endometrial lesions, including hyperplasias, polyps, and malignant tumors,[46,47] but the latter are not seen often enough to justify routine endometrial biopsies in this population.[48] None of the changes associated with tamoxifen are pathognomonic[49] and, accordingly, biopsies taken from women receiving tamoxifen therapy are diagnosed using terminology and diagnostic criteria identical to those used for patients not on tamoxifen. With respect to endometrial carcinomas developing in patients on tamoxifen, in two reported series a significant number of the cases were high-grade tumors associated with a poor prognosis,[50–52] but in others there was a great predominance of low-grade endometrioid adenocarcinomas,[53] and the former studies may reflect some selection bias.

Endometritis

Acute endometritis is usually seen in association with abortion, the postpartum state, or instrumentation. Gonococcal endometritis is rarely seen by the pathologist because of its very transient nature. Before making a diagnosis of acute endometritis, the pathologist should remember that neutrophils are normally present in the endometrium on days 26, 27, and 28.[54]

Chronic endometritis, characterized by an infiltrate of lymphocytes and plasma cells (often with an additional minor component of eosinophils[55]), may follow pregnancy or abortion, be the result of an intrauterine device (IUD), be associated with a submucosal leiomyoma, or be accompanied by mucopurulent cervicitis and/or pelvic inflammatory disease (PID).[56,57] The presence of chronic endometritis is associated with infertility/recurrent implantation failure. There, is some evidence that antibiotic therapy in these patients can result in improved outcomes in subsequent in vitro fertilization cycles, thus it is an important and clinically actionable diagnosis.[58] The most common symptoms are vaginal bleeding and pelvic pain, but most patients are asymptomatic.[57] It should be emphasized that lymphoid follicles, with or without germinal centers, are a normal occurrence in the functional layers of the endometrial mucosa and, therefore, should not be considered as evidence of chronic endometritis.[59] Therefore, identification of plasma cells constitutes the most important criterion for the diagnosis of chronic endometritis, whether by conventional criteria or—as suggested by some—by immunostaining the sections for immunoglobulins,[60] CD38,[61] VS38,[61] or syndecan-1 (Fig. 33.5).[62] However, it should be kept in mind that scattered plasma cells can be found in the absence of endometritis[63] and the demonstration of rare plasma cells with immunostains should not lead to overdiagnosis of endometritis. Clearly there remains important work to be done in refining the diagnostic criteria for chronic endometritis. The possibility of inflammation should be suspected—and plasma cells searched for—whenever there is an abnormal cyclic pattern, a focal mononuclear infiltrate, inflammatory cells in the glandular lumina, dense stroma, a stellate stromal pattern of proliferation, or foci of necrosis or calcification (Fig. 33.6). Glandular alterations commonly accompany the inflammatory reaction. The presence of neutrophils in the endometrial surface is a good predictor of PID, especially if combined with plasma cells in the endometrial stroma.[64]

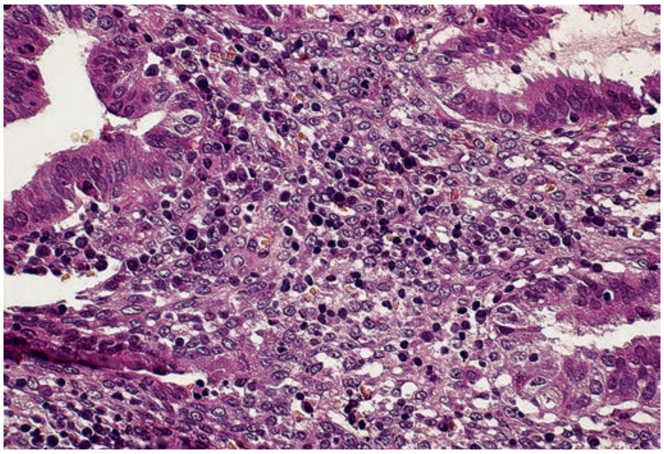


Figure 33.5 Chronic endometritis showing an inflammatory infiltrate rich in lymphocytes and plasma cells.

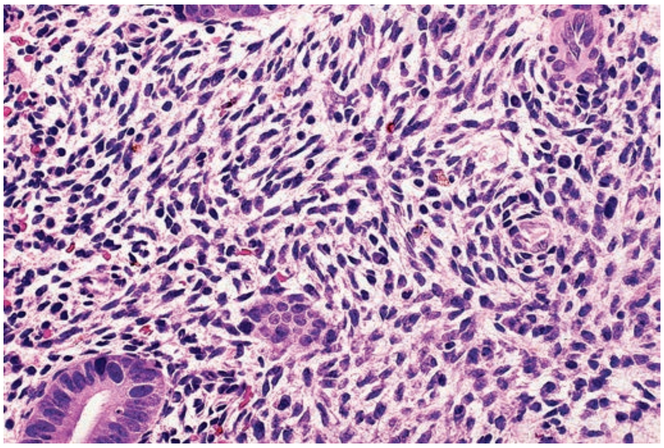


Figure 33.6 The oval to spindle and occasionally stellate shape of endometrial stromal cells is a clue to the diagnosis of chronic endometritis.

The myometrium is usually spared in most types of endometritis (sarcoidosis excluded, see later) unless the inflammation is very severe.

IUDs inserted for the purpose of contraception result in many biologic changes.[65,66] The most common change is focal or extensive chronic endometritis, which may be accompanied by necrosis and squamous metaplasia.[67,68] On occasion, the inflammation spreads through the fallopian tubes to produce PID and sometimes tubo-ovarian abscesses.[69,70] One of the agents involved in the inflammatory process is *Actinomyces* (Fig. 33.7).[71–73] The organisms can be detected in microscopic sections or in cytology preparations,[74] but care should be exercised in distinguishing them from pseudoactinomycotic radiate granules; the latter lack central branching filaments and diphtheroid forms.[75] The changes that can develop following the insertion of the Mirena coil were described in the previous section.

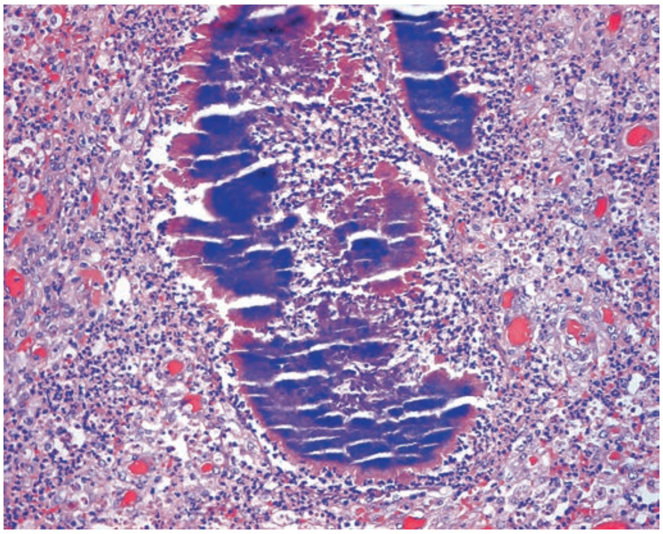


Figure 33.7 **IUD-Related Uterine Actinomycosis.** The disease had spread to the pelvic cavity.

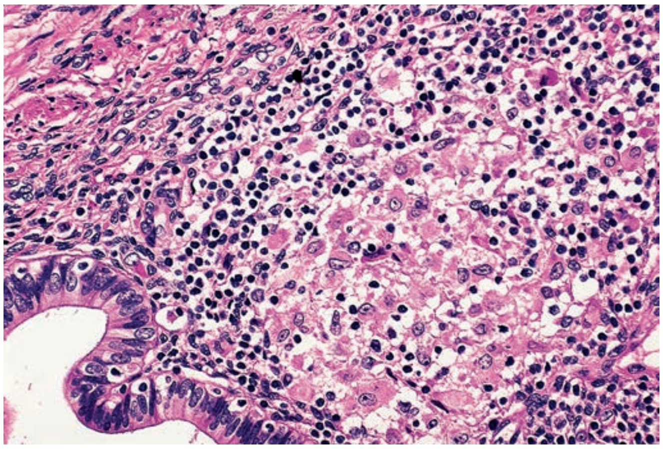


Figure 33.8 Noncaseating granuloma in endometrial mucosa consistent with sarcoidosis.

Pyometra refers to the accumulation of pus within the endometrial cavity. It is the consequence of the combined effect of obstruction and infection. Whiteley and Hamlett[76] reviewed 35 cases in postmenopausal patients. Only five were secondary to carcinoma; the remaining 30 were the result of benign cervical stricture originating from senile atresia, surgery, or cauterization.

Hematometra is the accumulation of blood within the endometrial cavity, usually as a result of cervical occlusion. This may lead to the disappearance of the endometrial mucosa and its replacement by sheets of lipid-containing histiocytic cells, a process known as *histiocytic* or *xanthogranulomatous endometritis* when diffuse and as *nodular histiocytic hyperplasia* when localized.[77,78] Sometimes the histiocytes are found to contain a yellowish-brown cytoplasmic pigment, in which case the term *ceroid-containing histiocytic granuloma* has been used.[79]

Endometrial tuberculosis is rare in the United States but still common in other parts of the world. Menstrual disturbances are common. The microscopic diagnosis is based on the demonstration of acid-fast bacilli in tubercles or culture. The presence of plasma cells and leukocytes probably results from secondary infection.[80] Tubercles may be missed unless multiple levels of curettings are examined. Since the granulomas tend to concentrate in the superficial functional layers of the endometrium, it is recommended that the biopsy be taken during the late secretory phase, and tissue should be submitted for culture as well as histopathologic examination.

Chlamydial infection has been identified through the immunohistochemical demonstration of chlamydial antigens in endometrial epithelial cells[81,82] or by polymerase chain reaction (PCR).[83] These cases are associated with severe acute and/or chronic inflammation. Plasma cells tend to be very numerous; as a matter of fact, it has been proposed that the presence of these cells is linked to *Chlamydia* infection.[84]

Viral infection of the endometrium is probably more common than generally suspected. Cytomegalovirus endometritis and diffuse papillomatosis (condyloma) have both been documented[85,86]; the former can have a granulomatous quality.[87]

Coccidioidomycosis of the uterus has been reported in the United States in a few cases as a localized infection; it probably results from a clinically inapparent and completely resolved primary lung infection.[88,89]

Postoperative granulomas of the endometrium have been described following endometrial ablation procedures; they may be thought of as the female counterpart of those seen in the prostate or bladder following transurethral resection (TUR).[90,91]

Malakoplakia of the endometrium has been reported, sometimes in a recurrent fashion and occasionally in association with endometrial adenocarcinoma.[92]

Sarcoidosis of the uterus occurs, but it remains a diagnosis of exclusion (Fig. 33.8).[93] In contrast to tuberculosis, the granulomatous reaction usually spreads to the myometrium.[94] Granulomatous endometritis can also follow hysteroscopic resection of the endometrium.[95]

Giant cell arteritis may involve the uterus and other genital organs of elderly women, either as an isolated finding (i.e. no systemic symptoms and normal acute phase reactants) or as part of a generalized process.[96–98] The former event is more frequent than the latter,[98] but sometimes female genital tract disease is the first manifestation of systemic periarteritis nodosa.[99] Over 90% of patients with isolated vasculitis of the myometrium have a nongranulomatous histology.[100]

Metaplasia

The endometrial glands and stroma are subject to a variety of metaplastic changes, many of them hormonally induced. They are often accompanied by hyperplastic changes in the endometrial glands but can occur independently from them and, therefore, need to be evaluated separately. They should not be regarded by themselves as evidence for the existence of a neoplastic process, but the presence of squamous metaplasia and mucinous metaplasia, in particular, should heighten awareness of the possibility of coexistent hyperplasia. Papillary syncytial and ciliated cell metaplasia are much less likely to be associated with hyperplasia. The endometrial metaplasias include:

1. **Squamous (morular) metaplasia**. This is most commonly encountered in hyperplastic endometrium but can be seen in association with leiomyoma or uterine polyps.[101] Frank keratinization is very rare *(ichthyosis uteri)*. A more common finding is the presence of nonkeratinizing squamoid cells occurring either diffusely (adenoacanthosis)[102] or in the form of berry-like aggregates (morules or morular metaplasia; Fig. 33.9).[103] Most are seen in premenopausal women, in those receiving exogenous hormones, or in association with polycystic ovary syndrome

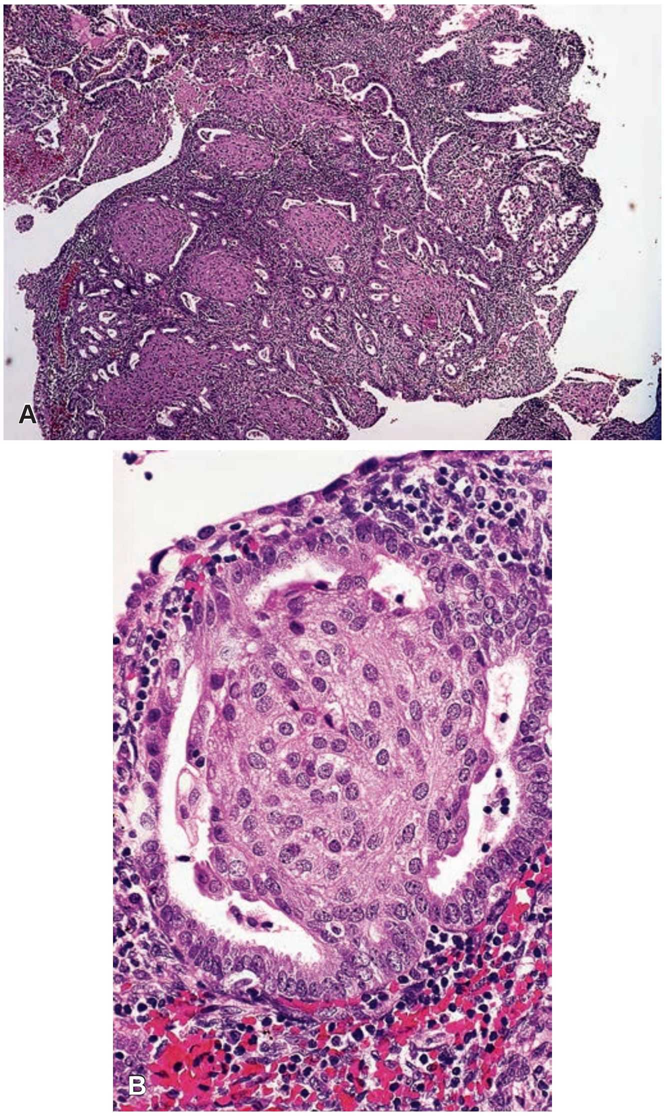


Figure 33.9 **A** and **B,** Squamous metaplasia of endometrium with morule formation.

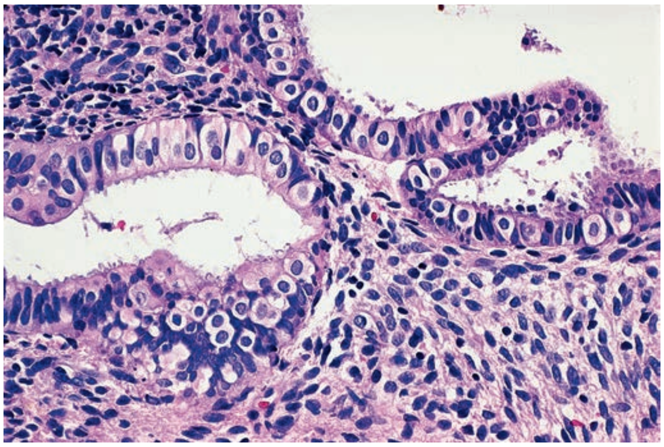


Figure 33.10 **Tubal Metaplasia of Endometrial Mucosa.** All three cell types that make up the normal mucosa of the fallopian tube can be recognized.

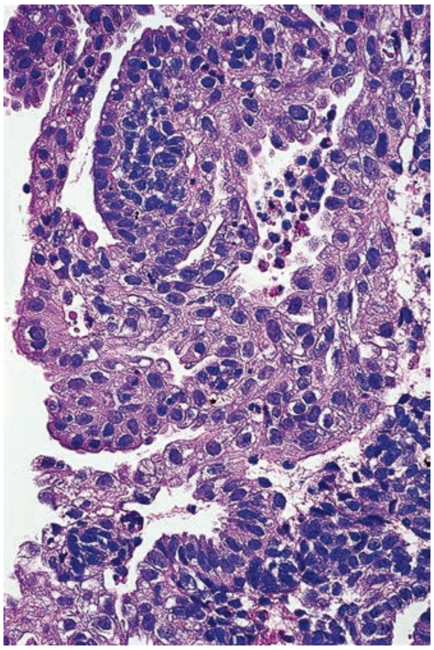


Figure 33.11 Papillary (syncytial) metaplasia of endometrium.

(PCOS).[104,105] This change is distinguished from well-differentiated endometrial adenocarcinoma with squamous metaplasia because of the benign appearance of the glandular elements, without glandular crowding or atypia. The morules represent a functionally inert tissue, in the sense of being devoid of sex hormone receptors and having an extremely low proliferation rate.[106] Surprisingly, they are immunoreactive for the intestinal transcription factor CDX2.[107]

2. **Ciliated cell (tubal) metaplasia**. Scattered ciliated cells are normally present in the endometrial mucosa; when markedly increased in number, the appearance resembles that of a fallopian tube, and the term listed earlier is used (Fig. 33.10).[108] Ciliated cell metaplasia is common in atrophic endometrium, to the point where it need not be commented on this setting. Occasionally the condition is associated with atypical nuclear features *("atypical tubal metaplasia")*, but even under these circumstances it does not seem to constitute a factor of significant risk for the development of endometrial adenocarcinoma.[109]
3. **Papillary syncytial metaplasia** (papillary syncytial change). This alteration is characterized by the presence of syncytial to papillary aggregates of eosinophilic cells along the surface epithelium (Fig. 33.11). It is often seen in association with endometrial breakdown.[110]
4. **Mucinous metaplasia**. In this condition, the endometrial mucosa reverts to a pattern morphologically, histochemically, and ultrastructurally similar to that of the endocervical mucosa (Fig. 33.12).[111,112] It is particularly common in endometrial polyps. The main differential diagnosis is with normal cervix or atypical mucinous proliferation of the endometrium/mucinous variant of endometrial adenocarcinoma.[113] With regards to the differential diagnosis with normal cervix, mucinous metaplasia can be recognized by its involvement of endometrial tissue (i.e. association with endometrial stromal cells and non-metaplastic endometrial glandular epithelium), and by the absence of reserve cells. Mucinous metaplasia should be focal, bland, and without glandular architectural features; in their presence a diagnosis of

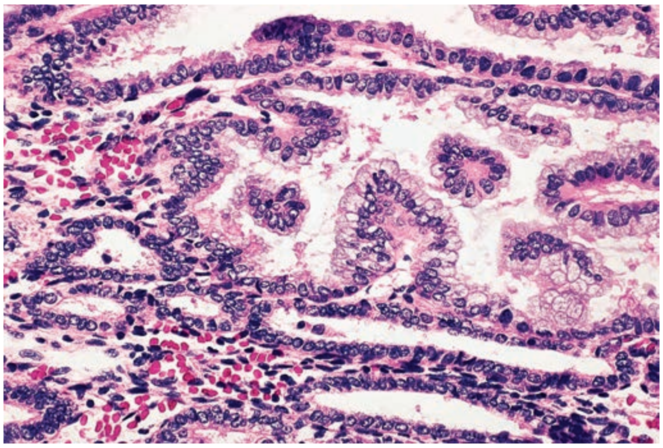


Figure 33.12 Mucinous Metaplasia of Endometrium. Note the basal location of the nuclei and the mucin-containing cytoplasm of the columnar cells.

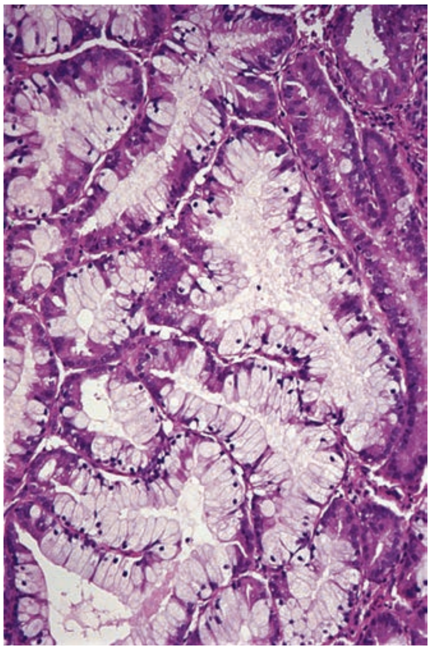


Figure 33.13 Clear Cell Metaplasia of Endometrium. The cytoplasm has a finely granular quality.

atypical mucinous glandular proliferation (discussed later) should be entertained.

5. **Eosinophilic (oxyphilic; oncocytic) metaplasia**. This is characterized by cells with abundant eosinophilic cytoplasm.[114] It is distinguished from atypical endometrial hyperplasia and the exceptionally rare oncocytic carcinoma by the absence of glandular crowding and atypical nuclear features.[115,116]
6. **Hobnail and clear cell metaplasia**. In these closely related metaplastic changes, the epithelium is clear, with tall cells having apically located nuclei (Fig. 33.13). The differential diagnosis is with clear cell (mesonephroid) adenocarcinoma.[115]
7. **Arias-Stella reaction.** See under Normal anatomy.
8. **Stromal metaplasia**. This includes the formation within the endometrial stroma of islands of smooth muscle,[117] cartilage,[118] and bone.[119] It should be noted that in most instances the presence of cartilage or bone is the result of retained fetal parts.[120]

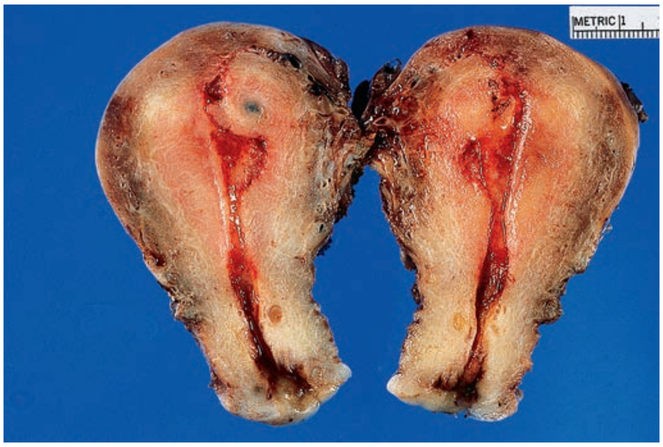


Figure 33.14 Gross Appearance of Uterus Involved by Adenomyosis. The wall is irregularly thickened and contains small hemorrhagic foci.

Adenomyosis and Endometriosis

Adenomyosis refers to the presence of islands of endometrial glands and stroma deep within the myometrium, whereas *endometriosis* is the term employed for the occurrence of endometrial tissue outside the uterus.[121] These two disorders are usually regarded as closely related, but their microscopic appearance is somewhat different. In most cases, adenomyosis is made up of the nonfunctional (basal) layer of the endometrium and is frequently connected with the mucosa. Endometriosis, on the other hand, is composed of the functional layers of the endometrium. As such, it may go through proliferative, secretory, and menstrual stages similar to those of its orthotopic counterpart. However, studies using conventional morphologic techniques, immunohistochemistry, and cell proliferation markers have shown that the endometriotic lesions are consistently more proliferative than the normally located endometrium, both during childbearing years and in postmenopause.[122–124] Adenomyosis is rare in postmenopausal women, except for the tamoxifen-associated cases, which tend to show stromal fibrosis, glandular dilation, and various metaplastic changes.[125]

Many pathogenetic theories have been proposed over the years for endometriosis: origin from congenital müllerian or wolffian rests, implantation of endometrium, lymphatic or hematogenous spread, and serosal metaplasia.[126,127] The finding of clonality, both within and a single endometriotic focus,[121,128] and across multiple foci from the same patient,[129] as well as the demonstration of oncogenic mutations in the epithelium of endometriosis,[130] lend support to the implantation theory but it should be noted that more than one pathogenetic mechanism may be involved.

Both endometriosis and adenomyosis may result in pelvic pain, characteristically associated with the menstrual period. Between 30% and 40% of women with endometriosis are infertile, the exact mechanism being still obscure. Exceptionally, adenomyosis may lead to rupture at the time of pregnancy.

Adenomyosis results grossly in an enlarged and globular uterus because of the myometrial hypertrophy that regularly accompanies it.[131,132] This enlargement is often asymmetrical. The diagnosis may be suspected on cut section in the presence of depressed small cystic lesions in obvious but ill-defined bulging zones of muscle hypertrophy (Fig. 33.14). Adenomyosis may form nodules, grossly, in which case the designation adenomyoma or adenomyotic nodule can be used.[133] Leiomyomas in utero with adenomyosis may themselves be involved by the process; distinction between leiomyoma with adenomyosis and adenomyoma/adenomyotic nodule is subjective but is made

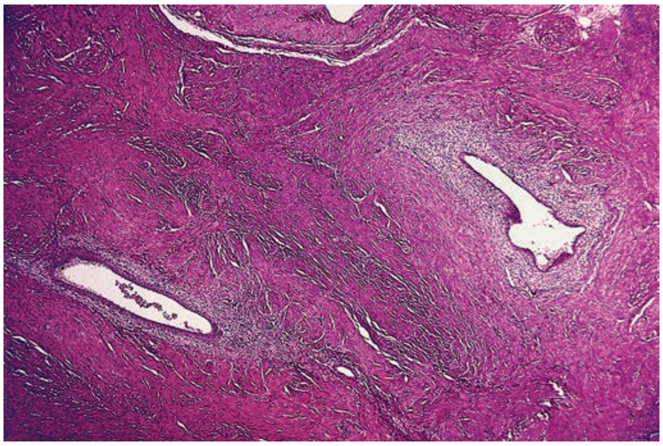


Figure 33.15 Intramyometrial foci of endometrial glands and stroma in adenomyosis.

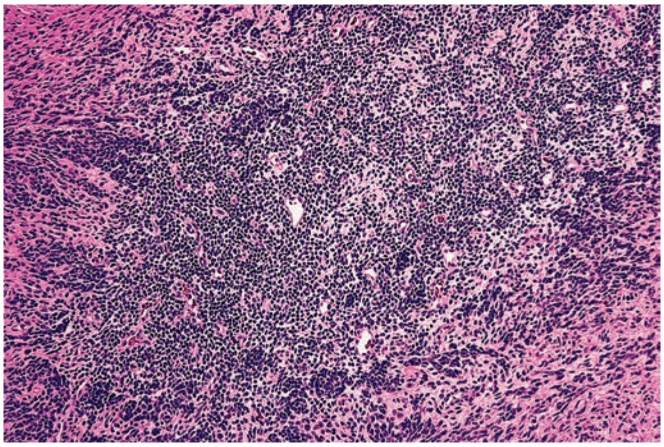


Figure 33.16 **So-Called Stromal Adenomyosis.** An ill-defined island of endometrial stroma is deeply embedded within the myometrium.

based on the endometrial glands and stromal being only at the periphery of the nodule in the former while they are present throughout the latter.

Microscopically, the diagnosis of adenomyosis depends on the thresholds used by the individual pathologist, some of which are very liberal indeed.[134] The interface between endometrium and myometrium is normally an irregular one, without interposition of a submucosal layer; invaginations of the endometrial basal layer into the superficial portions of the myometrium should be regarded as a normal finding. By convention, the diagnosis of adenomyosis should be reserved for those cases in which endometrial glands and stroma are seen in the myometrium at a distance of at least one low-power field from the endometrial–myometrial junction (Fig. 33.15).

Microscopically, the endometrium of adenomyosis usually has a proliferative appearance, consistent with its basal layer nature. When the normally located endometrium is in the secretory phase, this is also true for one-fourth of the foci of adenomyosis.[135] These foci can be involved by any of the diseases affecting the orthotopic endometrium, including hyperplasia and adenocarcinoma.[136] It is important to recognize this phenomenon, lest a case of in situ or superficial endometrial adenocarcinoma associated with similar changes in the foci of adenomyosis be misinterpreted as a deeply invasive malignancy.[137] Involvement of adenomyosis by endometrial adenocarcinoma does not seem to affect outcome.[138]

Vascular involvement may be present and should not be overinterpreted as a sign of malignancy.[139]

Some small islands of adenomyosis are made up predominantly of endometrial stroma (*stromal adenomyosis*, *incomplete adenomyosis* or *adenomyosis with sparse glands*; Fig. 33.16)[140]; however, any sizable intramyometrial focus composed entirely of endometrial stroma is likely to represent an endometrial stromal sarcoma.[141]

Endometriosis, which is thought to occur in 1%–7% of women in the United States,[142,143] is a major cause of pelvic pain and subfertility.[144] It can be located in the cervix, vagina, vulva, rectovaginal septum, ovary, fallopian tubes, uterine ligaments, appendix, small and large bowel, bladder and ureters, pelvic peritoneum, hernia sacs, lymph nodes, kidney, and skin, and even within skeletal muscles, peripheral nerves, pleura, lung, and nasal cavity (Figs. 33.17 and 33.18). The specific features as they pertain to the various sites are discussed in the respective chapters. Spontaneous cutaneous endometriosis is limited to the umbilicus and inguinal area.[145] In other locations, such as the lower abdominal wall, it practically always arises in surgical scars (particularly those from cesarean sections).

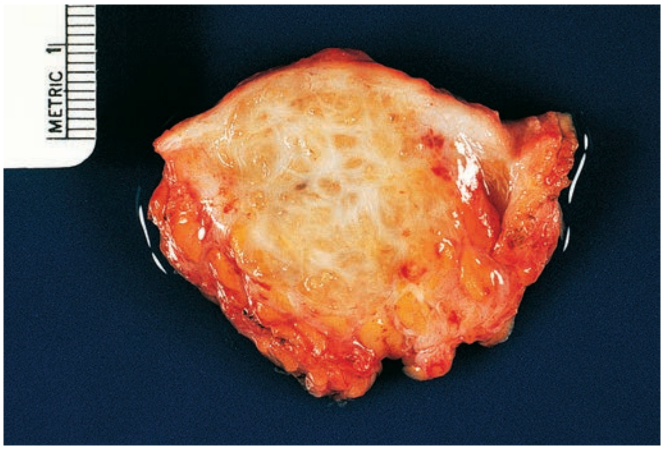


Figure 33.17 Gross appearance of endometriosis involving the anterior abdominal wall.

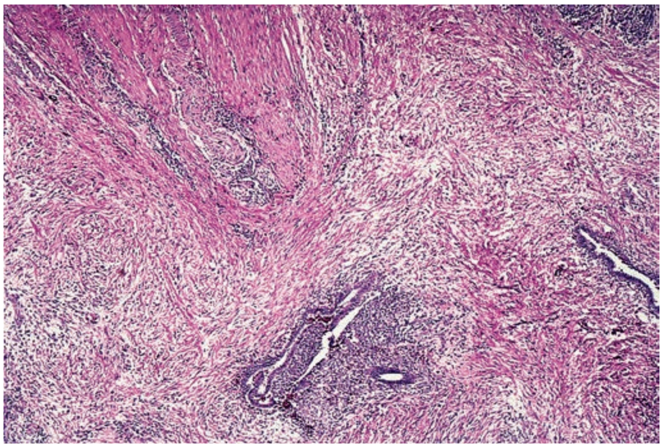


Figure 33.18 Endometriosis involving the umbilical region.

Grossly, endometriosis appears as bluish cystic nodules, often surrounded by fibrosis. Exceptionally, it may present as multiple polypoid masses grossly simulating a neoplastic process (*polypoid endometriosis* or *endometriotic polyposis*).[146,147] These masses can be located in the colon, ovary, uterine serosa, ureter, fallopian tubes, and several other sites.[147]

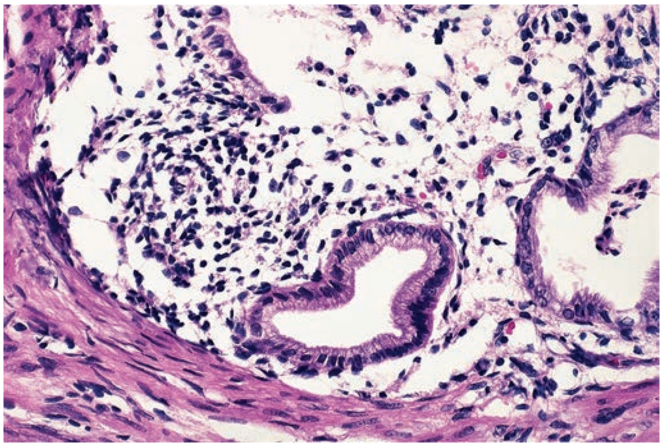


Figure 33.19 So-Called Endocervicosis. The stroma has an endometrium-like quality, but the glands are of endocervical type.

Microscopically, endometrial glands and stroma are seen, often embedded in a dense fibrous mass exhibiting signs of fresh and old hemorrhage.[148] The stromal component of endometriosis can undergo smooth muscle metaplasia.[149] Along those lines, it is still being argued whether the nodular lesion resembling a miniature uterus, which can be found in several places within the peritoneal cavity (ovary, small bowel, etc.), is a peculiar variant of endometriosis with smooth muscle metaplasia of the stroma or a malformation of the müllerian ducts.[131,150,151]

Other morphologic variations in the theme of endometriosis, some of which can be of confusing interpretation, include the presence of stromal micronodules, stromal elastosis, prominent myxoid changes, perineurial invasion, and regeneration of the surrounding skeletal muscle.[152–155] Endometriotic foci can undergo prominent mucinous metaplasia, a change that can result in a mistaken diagnosis of well-differentiated mucinous adenocarcinomas. Such change has been interpreted as a metaplasia toward endocervical-type epithelium and designated as *endocervicosis* (Fig. 33.19).[148]

Although well-documented cases of endometriosis of lymph nodes exist, most cases so designated are made up of glands lined by ciliated or nonciliated cuboidal epithelium unaccompanied by stroma, limited to the capsule or cortical area of the node[156]; as such, they are more reminiscent of fallopian tube than endometrial epithelium and are better designated as *endosalpingiosis*. They have been found in approximately 14% of nodes in females but practically never in males.[157]

Endosalpingiosis is particularly frequent in the pelvic peritoneum in connection with low-grade ovarian serous tumors. It can also present in the form of a florid cystic mass and involve the uterine wall in a transmural fashion.[158,159]

The combination of endometriosis with endocervicosis and/or endosalpingiosis is sometimes referred to as müllerianosis.[160]

Endometriosis, like adenomyosis, is subject to any of the metaplastic, hyperplastic, and atypical changes that may supervene in the orthotopic endometrium.[162] More importantly, it may undergo malignant transformation.[163,164] The most common forms are endometrioid and clear cell carcinoma,[146,165–167] but endometrial stromal sarcoma, carcinosarcoma, and adenosarcoma have also been reported.[168] Benign and borderline tumors of either serous or endometrioid nature can also develop, both from conventional endometriosis and from endosalpingiosis.[169–172] The most common site for endometriosis-related neoplasms is within endometriotic cysts of the ovary, with pelvic peritoneum, rectovaginal septum, intestinal wall, and other sites being much less common.[167,173]

The treatment of endometriosis may be hormonal or surgical depending on the circumstances.[174] It is believed that the laparoscopic ablation of minimal and mild endometriosis enhances fecundity in infertile women.[175]

Dysfunctional Uterine Bleeding

Bleeding not associated with an organic cause in women of childbearing age belongs to the large and somewhat nebulous category known as **dysfunctional uterine bleeding**. Examination of specimens obtained on D&C or endometrial biopsy from patients with dysfunctional uterine bleeding is done primarily to exclude neoplasia/preneoplastic changes, or other pathology that may be causing the abnormal bleeding, such as an endometrial polyp. A wide range of changes can be seen in the endometrium that differ from normal proliferative or secretory endometrium, but attempts by pathologists to classify these changes into categories that can guide treatment have been largely unsuccessful. On a personal note, it was a disheartening experience as a senior surgical pathologist to talk to a group of younger gynecologists and find out how little clinical value there was in my carefully crafted reports describing minor morphologic changes in the endometrium associated with dysfunctional uterine bleeding! What follows is a description of some of the histologic abnormalities that may be encountered in endometria sampled for dysfunctional uterine bleeding, but the suggested diagnostic terminology is provided in the upcoming section on “Curettage and biopsy.”

The presence of fibrin clumps in the endometrial stroma (a finding not usually present in the normal menstrual endometrium),[123] the identification of fragmented pieces with dense stromal cellularity (a process known as *stromal crumbling*), and the presence of an increased number of apoptotic bodies at the base of the glands (so-called Benirschke granules)[176] may all be seen. Another type of defect seen in the ovulatory group of bleeders is known as *irregular shedding of the endometrium*. The term refers to a regularly recurring menorrhagia in which the bleeding phase of the cycle requires 7 days or more for completion, without subsequent prolongation of the cycle. This is due to a lag in the shedding of the secretory endometrium, which is normally completed by the fourth day of menstruation.[177] Tissue obtained five or more days after the onset of menstrual bleeding shows retained secretory endometrium in addition to fragmented menstrual and/or early proliferative endometrium.

The term *membranous dysmenorrhea* has been used for a rare condition characterized by the painful passage of an endometrial cast of the uterus during the first few days of menstruation. This cast has the microscopic appearance of decidua. The disease is thought to result from a hyperprogestational response and may be induced by the administration of high doses of progesterone.[177]

Anovulatory cycles result in exuberant *disordered proliferative endometrium*, recognized by irregularity of glandular outlines, with more complexity of gland profiles than is encountered in normal proliferative phase. There is not sufficient glandular crowding to warrant a diagnosis of endometrial hyperplasia. The glandular epithelial cells lack atypia and show nuclear features similar to those of normal proliferative glands. There may be abortive subnuclear vacuoles and apoptotic bodies within glands. Anovulatory cycles are common in PCOS but also very common at puberty and in the perimenopausal period. Distinction between disordered proliferative endometrium and normal proliferative endometrium, on one hand, and endometrial hyperplasia without atypia on the other, is subjective. The general rule of diagnosing an abnormal state only when changes are clear-cut can be applied in this situation; only diagnose disordered proliferative endometrium when the architecture of the glands is too abnormal to fit into the spectrum of

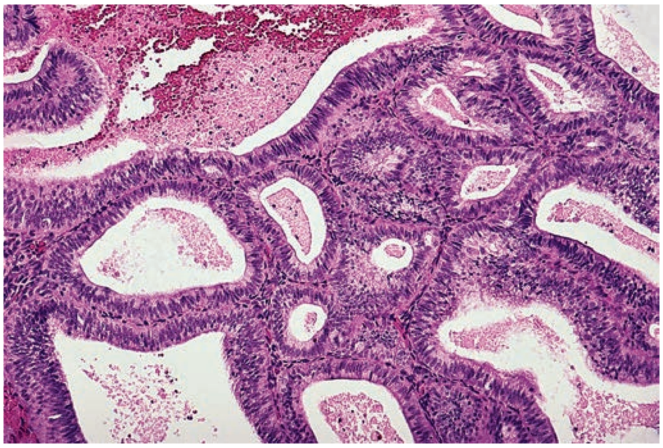


Figure 33.20 **Endometrial Hyperplasia Without Atypia.** There is mild irregularity of glandular architecture, and crowding.

normal proliferative endometrium. Distinction between disordered proliferative endometrium and hyperplasia without atypia will be discussed next.

Endometrial Hyperplasia Without Atypia, Atypical Hyperplasia, and Variants

Endometrial hyperplasia is recognized by increased gland-to-stroma ratio and glandular architectural irregularity and complexity. There have been many classifications of endometrial hyperplasia over the years, but the one in current use is the one put forward by the World Health Organization (WHO) in 2014.[124]

Endometrial hyperplasia without atypia occurs as a result of unopposed estrogenic stimulation of the endometrium and is on a continuum with disordered proliferative endometrium. There is glandular branching, irregularity, and crowding (Fig. 33.20). The diagnostic threshold for diagnosis of endometrial hyperplasia without atypia, rather than disordered proliferative endometrium, is highly subjective, but at the point where glands predominate over stroma, a diagnosis of endometrial hyperplasia without atypia is appropriate. In the past, endometrial hyperplasia was subdivided into simple and complex hyperplasia, based on the degree of glandular architectural complexity; this is no longer done as it is not a clinically relevant subclassification. The risk of progression to carcinoma with endometrial hyperplasia without atypia is low (1%–3%).[178] The chief differential diagnosis is with atypical hyperplasia, and this is based on the assessment of cytologic atypia; the criteria for recognition of atypia are presented in the next section.

Atypical hyperplasia is the precursor lesion of low-grade endometrioid adenocarcinoma. It shows glandular crowding and irregularity in addition to cytologic atypia. The nuclear atypia is characterized by enlargement, rounding, pleomorphism, and presence of nucleoli. Quite apart from these descriptive terms, the presence of cytologic atypia is most reliably recognized by comparison of the cytologic features in the hyperplastic focus to those of proliferative endometrial glandular epithelial cells outside the area of hyperplasia (Fig. 33.21).[124,179] This approach to diagnosis of cytologic atypia, proposed by Mutter and colleagues, has enhanced the reproducibility of the diagnosis of atypical hyperplasia.[126,180] It is exactly equivalent to the way we evaluate colonic biopsies for adenomatous change and, as is the case for colonic adenomas, the cytologic atypia within the atypical hyperplasia reflects a clonal proliferation of cells with some but not all the mutations necessary for transformation to carcinoma. One cautionary note is warranted on using this approach to diagnose cytologic atypia; if there is coexistence of proliferative endometrium and inactive endometrium, there are going to be differences between the nuclei in the two areas, but this does not reflect premalignant change. The recognition of atypia is based on cytologic differences between the endometrium in the hyperplastic focus and proliferative endometrium in non-hyperplastic endometrium.

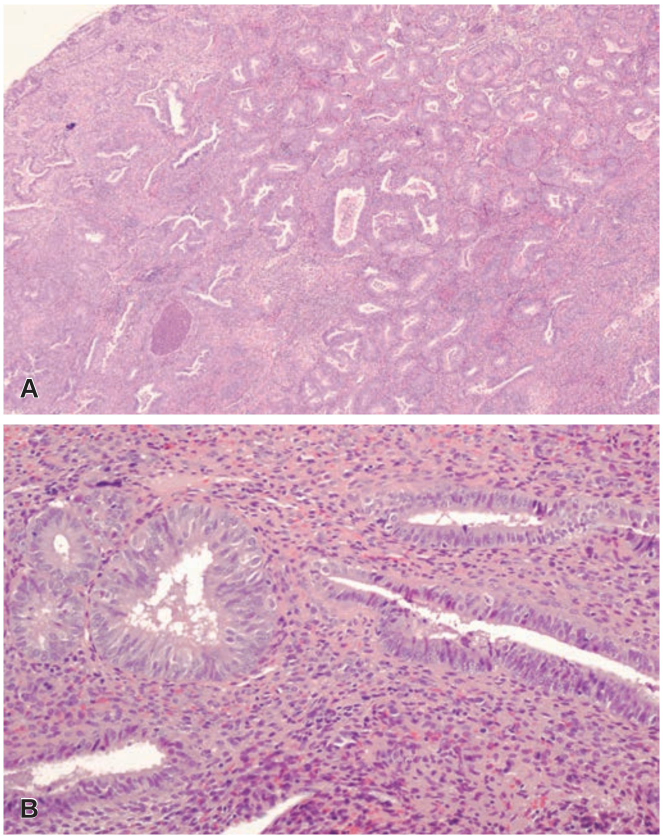


Figure 33.21 **A,** Endometrial hyperplasia with atypia, in a polyp; **B,** low-power, showing the glandular crowding, and **C,** high-power, from the edge of the hyperplastic focus, showing the cytologic difference between the atypical epithelium (on the left) and non-atypical epithelium.

The presence of metaplastic changes complicates the interpretation of cytologic features, and we can offer no easy to solution to this vexing, recurrent problem: is this atypical hyperplasia or hyperplasia without atypia, but with metaplastic changes? This is further complicated by the frequent coexistence of metaplasia and atypical hyperplasia. As a practical guideline, the greater the degree of glandular crowding, the more likely it is that the cytologic changes are atypical.

Endometrioid intraepithelial neoplasia (EIN) is an alternative diagnostic term for atypical hyperplasia. The EIN terminology was proposed by Mutter, who developed the much improved diagnostic criteria for recognition of premalignant change in the endometrium.[134,179,181] What has happened is that there has been universal adoption of the new criteria for diagnosis of endometrial premalignancy, but less uniform adoption of EIN terminology. Thus, at this time, atypical hyperplasia and EIN are completely synonymous diagnostic terms, reflecting the same diagnostic criteria.

The incidence of carcinoma in women with atypical hyperplasia has been in the neighborhood of 15% and has reached 30% in some series.[125,178,182,183] A significant minority of women who have a diagnosis of atypical hyperplasia made on biopsy or curettings will have adenocarcinoma (almost invariably low grade and minimally or non-myoinvasive) diagnosed on the subsequent hysterectomy specimen.[184]

The distinction between a case of atypical hyperplasia with severe architectural and cytologic atypia and a well-differentiated adenocarcinoma can be very difficult, largely because of the fact that endometrial hyperplasia and carcinoma represent different points in a disease continuum at the morphologic, ultrastructural, immunocytochemical, and molecular genetic levels.[139,185,186] A careful reading of the landmark study by Longacre and colleagues is recommended.[187] Although more than 20 years have passed since the publication of this paper, it remains a beautiful example of good study design, and the data produced continue to inform everyday practice. The presence of confluence of glands, such there are no longer small glands surrounded by stroma, or a papillary/villoglandular architecture are features supporting a diagnosis of well-differentiated adenocarcinoma. On biopsy or curettings it has been recommended that the diagnosis of "atypical hyperplasia, cannot exclude low-grade adenocarcinoma" be used for those cases where the features are intermediate between atypical hyperplasia and grade 1 endometrioid adenocarcinoma, and we endorse this view. We do not recommend the use of this terminology for hysterectomy specimens.

There is an increasing trend to treat atypical hyperplasia or even low-grade adenocarcinoma with high-dose progestin therapy,[188] so as to avoid hysterectomy and preserve fertility. The interpretation of findings in follow-up biopsies is complicated by prominent progestational effects, including squamous and mucinous metaplasia of the epithelium and stromal decidual reaction. In our experience, there are three possible diagnostic results for these follow-up specimens: either 1. There is no evidence of residual hyperplasia, 2. There is residual hyperplasia with treatment effects (metaplasia and decidual change), or 3. There is residual hyperplasia that shows no treatment effects, and may even show more severe atypia or progression to frank carcinoma, when compared to the pretreatment biopsy.

Atypical mucinous glandular proliferation of the endometrium is considered to be a precursor of mucinous carcinoma. It is recognized based on glandular crowding and complexity with prominent mucinous metaplasia of the glandular lining cells, but these cells can show minimal cytologic atypia.[124] We have previously acknowledged the difficulty in distinguishing between atypical hyperplasia and carcinoma, but it is even more difficult for mucinous proliferations. The likelihood of adenocarcinoma in the hysterectomy after a diagnosis of atypical mucinous glandular proliferation was 45% in a recent study.[189] Atypical mucinous glandular proliferation of the endometrium should therefore be considered to be a premalignant lesion with significant chance of progression or coexistent carcinoma, with hysterectomy being the preferred treatment. Awareness of atypical mucinous proliferation of the endometrium is important as we have seen this premalignant change misdiagnosed as normal endocervical tissue.

Papillary proliferation of the endometrium (PPE) was first described by Lehman and Hart[190] and is characterized by a prominent papillary architecture, with papillae covered by epithelial cells with minimal cytologic atypia (Fig. 33.22). There is a variation from small foci of simple papillae with short nonbranching stalks to extensive complex papillae with elongated stalks and branches. The absence of significant nuclear atypia separates this from carcinoma. The lining epithelium consists of a single layer cells with pale eosinophilic or mucinous cytoplasm, sometimes ciliated. Papillary proliferation frequently involves an endometrial polyp. PPE has subsequently been subdivided into simple and complex forms, by Ip et al.[191] Simple PPE is characterized by short, predominantly nonbranching stalks (occasional secondary branches may be seen) localized to 1 or 2 foci involving the surface of polyps, non-polypoid endometrium, or within cystically dilated glands, or involvement of <50% of a polyp. Complex PPE consists of complex papillae (short or long stalks with frequent secondary and complex branching) and/or diffuse involvement (three or more foci within a specimen, or involvement of >50% of polyp). Complex PPE, in particular, often coexists with conventional atypical hyperplasia or even carcinoma. The clinical significance of simple PPE is considered equivalent to that of hyperplasia without atypia, while complex PPE is equivalent to atypical hyperplasia, based on a limited number of reported cases.[191]

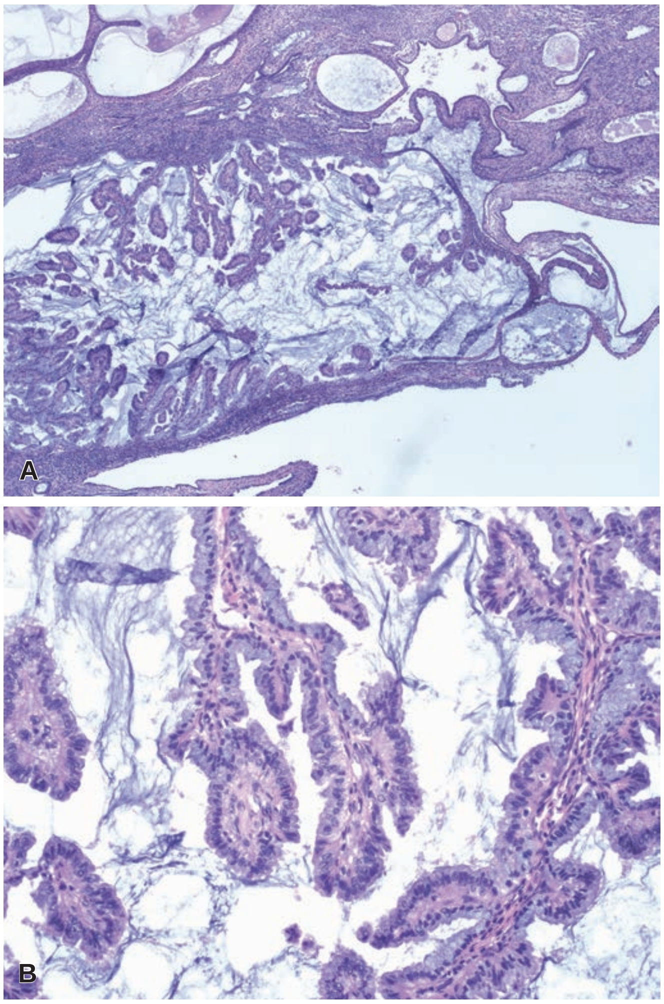


Figure 33.22 Papillary Proliferation of the Endometrium (PPE). **A,** PPE in an endometrial polyp; **B,** bland mucinous epithelial cells cover the papillae. This single focus, confined to a polyp, is simple PPE.

The term **(atypical) secretory hyperplasia** has been applied to a pattern of architectural abnormalities and cellular atypia within a secretory endometrium, with the atypical glands resembling those seen in the sixteenth to the seventeenth day of the normal cycle.[128,132,192] This change should be distinguished from the Arias-Stella reaction and from hormonally treated conventional endometrial hyperplasia. The natural history of this condition is not well known, but involution appears to be relatively common when the background endometrium also shows secretory changes.[192] Normal secretory endometrium appears relatively crowded, and it is best to be conservative in diagnosis of hyperplasia in the setting of secretory endometrium.

Curettage and Biopsy

Tissue from the endometrial cavity taken for diagnostic purposes was traditionally obtained by *dilation* of the cervical canal and *curettage* of the endometrial cavity (D&C). Information about endocervical extension of an endometrial neoplasm can be obtained by performing a *fractional curettage* (i.e. a separate sampling from the endometrial and endocervical cavities during the same procedure). The endocervical specimen should be obtained first so as to minimize contamination from the endometrium. However, even when this precaution is taken, small isolated tumor fragments may be found in endocervical curetting specimens in cases where there is no infiltration of the cervix by tumor. Therefore, the presence of endocervical extension of a tumor can only be diagnosed if cancer and normal endocervical glands are seen *in the same tissue fragment*. Otherwise, simply record the presence of carcinoma in the material submitted from the endocervix and let the clinician decide whether this is significant on the basis of the findings at the time of curettage.

Endometrial biopsy has emerged as an alternative to D&C for the evaluation of the endometrium.[127] It can be performed safely in the office (but causes significant discomfort and pathologists should not be cavalier in recommending resampling of the endometrium). Biopsy may also be carried out under hysteroscopic guidance.[121] A meta-analysis study with the use of the Pipelle showed a detection rate for endometrial adenocarcinoma of 99.6% in postmenopausal women and 91% in the premenopausal group.[136] Another issue is the accuracy of the grading of endometrial carcinoma done in a biopsy when compared with that seen in the hysterectomy specimen. In one study, the concordance was 45% for grade I, 63.3% for grade II, and 75.6% for grade III, the overall concordance being 64.5%.[193] Even comparing the diagnosis of low-grade (grade I or II) versus high-grade (grade 3) carcinoma in biopsy/curettings versus hysterectomy, there remains distressing variation, but with some improvement (kappa—0.7).[194] Histotype diagnosis (i.e. endometrioid, serous, clear cell, etc.) shows only moderate agreement between biopsy/curettings and hysterectomy (kappa—0.44).[194]

A curious artifact that can be seen in hysteroscopically assessed tissue is *pseudolipomatosis*, a condition analogous to its more common counterpart in the gastrointestinal tract. It results from air or gas entering into the endometrial mucosa and simulating fatty infiltration.[195]

An exceptionally rare occurrence is the failure to find tumor in a hysterectomy specimen following a diagnosis of adenocarcinoma in an endometrial biopsy. This distressing event, which has been referred to as *vanishing endometrial carcinoma* (in analogy to the same phenomenon as described in the prostate) is probably explained by the very minute size of the tumor, most or all of which has been removed by the biopsy procedure.[196]

The language used in reporting on endometrial biopsies where there are only benign findings is highly variable from pathologist to pathologist, in contrast to the standardized language and formatting we use for cancer specimens. There remain pathologists who believe that they are being called upon to determine whether ovulation has occurred, even though this has not been an expectation for more than a decade, while other pathologists report in great morphologic detail on biopsies taken for infertility when their clinical colleagues only want reassurance that there is no polyp, endometritis, or hyperplasia/carcinoma. Please do discuss with clinicians their needs, so that you can better serve your patients by providing clinically relevant information in your surgical pathology reports. We do believe, however, that more uniform reporting of benign endometrial biopsy specimens will enhance the value of our reports, improving their comprehensibility. A guideline for uniform diagnostic categories to use in reporting endometrial biopsies has been proposed by the Canadian Gynecological Pathology Special Interest Group (Box 33.1); when trialed in practice, more than 90% of cases could be reported using this template, in a range of practice scenarios.

A final comment is called for on the criteria for insufficiency in an endometrial biopsy or curetting. Remember that the expected finding in a postmenopausal woman is scant inactive or atrophic endometrium. The presence of strips of atrophic endometrium is normal in this clinical scenario and should not be considered insufficient for diagnosis, a diagnosis that should be reserved for instances where there is no endometrial tissue sampled. Sakhdari et al. have suggested that the presence of 10 or more endometrial strips constitutes an adequate sample, while fewer than 10 strips is suboptimal (negative predictive values in the group with an adequate sample was >99% versus approximately 80% in the group with a suboptimal sample).[197] This finding should be validated independently, but it appears that there are three categories of samples: adequate, benign but suboptimal because of their scanty nature (<10 strips of endometrial epithelium), and insufficient for diagnosis (no endometrial tissue sampled).

Box 33.1 Suggested terminology for signing out benign endometrial biopsy or curetting specimens

Diagnosis (choose one or more)

- Non-diagnostic sample (no endometrial tissue present)
- Scant fragments of inactive endometrial surface epithelium and/or stroma; this is a suboptimal specimen for histopathological assessment and may not be representative*
- Inactive/atrophic endometrium
- Proliferative endometrium
  - Normal proliferative
  - Weakly proliferative
  - Disordered proliferative
- Secretory endometrium
  - Normal secretory
    - Date ___
    - Polypoid secretory endometrium
  - Irregular secretory
- Menstrual endometrium
- Endometrial polyp(s)
- Endometrial hyperplasia without atypia
- Chronic endometritis
- Changes consistent with exogenous hormonal therapy
  - Progestin
  - Progesterone receptor selective agonist
  - Oral contraceptive
- Products of conception
  - Chorionic villi
  - Chorionic plate
  - Chorionic membranes
  - Implantation site trophoblast
  - Exaggerated implantation site
  - Embryonic/fetal tissue
- Pregnancy-related endometrial changes
- Pregnancy-related endometrial changes only; no products of conception identified
- Placental site nodule/remote implantation site
- Adipose tissue, mesothelium—lined tissue or other extrauterine tissues present

*Fewer than 10 strips of epithelium in an endometrial biopsy or curettage specimen is suboptimal and is associated with decreased sensitivity and negative predictive value.[197]

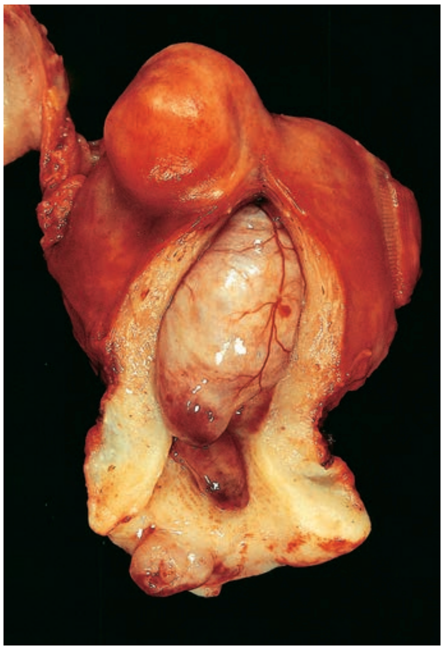


Figure 33.23 **Huge Endometrial Polyp Filling the Endometrial Cavity.** There is also a smaller endocervical polyp and a subserosal leiomyoma. (Courtesy Dr. Pedro J Grases Galofrè; from Grases Galofrè PJ. *Patologia ginecològica. Bases para el diagnòstico morfològico*. Barcelona: Masson; 2002.)

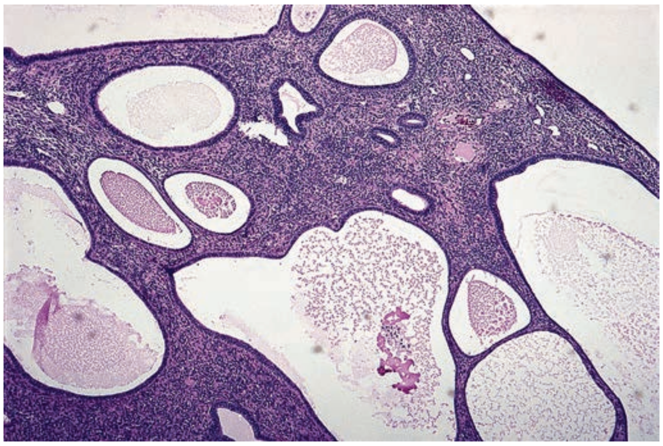


Figure 33.24 Low-power appearance of endometrial polyp showing cystically dilated glands and a fibrous stroma with thick-walled vessels.

Tumors

Endometrial Polyps

Endometrial polyps protrude into the endometrial cavity and often exhibit changes secondary to vascular insufficiency or prolapse (Fig. 33.23). They consist of epithelial and stromal components, and a key to recognition in fragmented specimens, e.g. endometrial curettings, is the altered cellularity of the stroma compared to normal endometrium, with the polyp stroma usually showing reduced cellularity with a more "fibrous" appearing and spindle cell stroma, compared to normal endometrial stroma. The glands usually show some degree of cystic change. They may be lined by an active pseudostratified epithelium containing mitotic figures or, in the postmenopausal patient, by a flat, inactive epithelium (Fig. 33.24). The abnormal glandular architecture may raise the possibility of endometrial hyperplasia, but the absence of glandular crowding excludes the diagnosis of hyperplasia. Note that hyperplasia (without atypia or atypical) or carcinoma may be present in an endometrial polyp and are diagnosed using the same criteria as are used in the absence of a polyp.

The glands and stroma of the polyp are unresponsive to progesterone stimulation and retain their integrity throughout the menstrual cycle. The frequent coexistence of endometrial polyps and endometrial hyperplasia points to a shared pathogenesis for these two lesions. The clinical significance and management of atypical hyperplasia are the same irrespective of whether it involves or is confined to an endometrial polyp.[198]

Exceptionally, the stroma of endometrial polyps contains scattered atypical (bizarre) cells.[199,200]

Endometrial polyps occur with increased frequency after tamoxifen exposure. These are characteristically multiple, large, and fibrotic and may exhibit stromal decidualization and mucinous metaplasia.[201–203]

With the increasing use of hysteroscopy, we frequently receive endometrial biopsies of polypoid endometrium that microscopically is seen to be normal secretory endometrium. Unfortunately there is no uniform diagnosis used for this relatively common scenario, and proposed diagnoses include "polypoid secretory endometrium" or "secretory pseudopolyp."

Endometrial polyps having smooth muscle fibers (not connected with blood vessel walls) in addition to the customary glands and stroma are designated as **adenomyomatous polyps** (polypoid adenomyomas) (Fig. 33.25).[204] In order to make this diagnosis, the smooth muscle should be integral to the polyp; benign endometrial polyps when they start to prolapse often draw smooth muscle into the polyp stalk, and this phenomenon does not warrant diagnosis as adenomyomatous polyp. They have a characteristic hard consistency and a grayish color.

An important variation on the theme is the **atypical polypoid adenomyoma**.[205–208] These tend to occur in premenopausal women (average age, 40 years) and present with abnormal uterine bleeding (Fig. 33.26). Some are associated with Turner syndrome.[209] Microscopically, they are identified by the fact that the glands occurring between the endometrial stroma and smooth muscle exhibit varying degrees of hyperplasia and atypia (often with squamous morular metaplasia), sometimes approaching the appearance of low-grade carcinoma (Fig. 33.27).[210] Recognition is important to avoid misdiagnosis as adenocarcinomas with myometrial invasion. The behavior reflects the degree of complexity and atypia of the epithelial component, which can range from atypia without hyperplasia, to atypical hyperplasia and, on occasion, frank carcinoma of low-grade endometrioid type.

At the molecular level, atypical polypoid adenomyomas share several alterations with hyperplasias.[211]

Endometrial Carcinoma

General and Clinical Features, Including Molecular Subtypes

Carcinoma of the endometrium is the most common gynecologic malignancy in developed countries.[212] The highest incidence rates are in the United States and Canada, but in recent years there has been a decline in incidence and mortality. It typically occurs in elderly individuals, 80% of the patients being postmenopausal at the time of diagnosis.[213] However, it can occur in any age group and has even been reported in association with intrauterine pregnancy.[214] Most endometrial adenocarcinomas occurring in women aged 40 years or younger are of endometrioid type, well to moderately differentiated, and early stage disease.[215] Conversely, tumors of elderly patients are more likely to be grade 2 or 3 and to have more advanced disease at the time of diagnosis.[216]

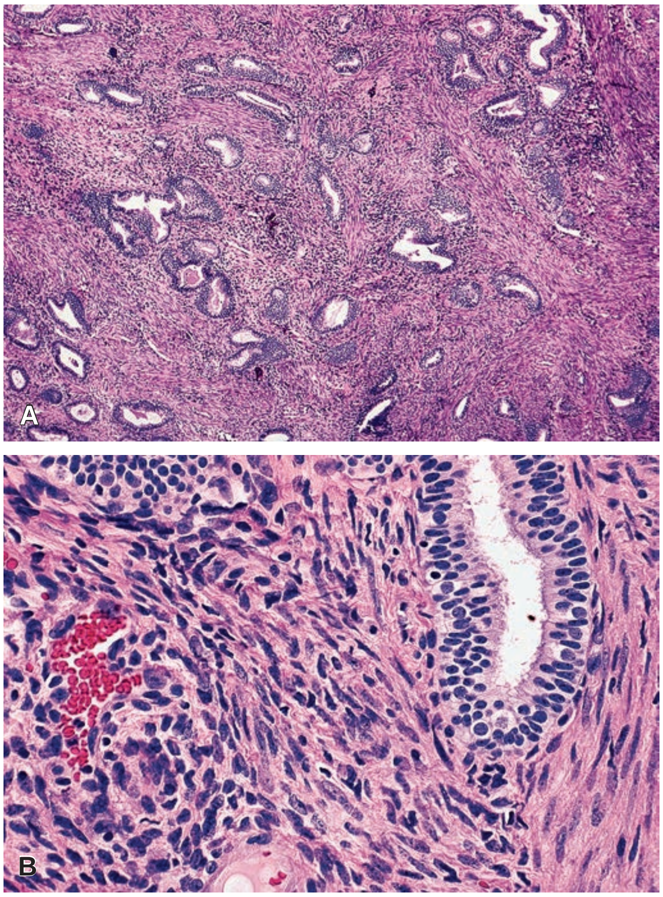


Figure 33.25 **A** and **B,** Low- and high-power appearance of adenomyomatous polyp.

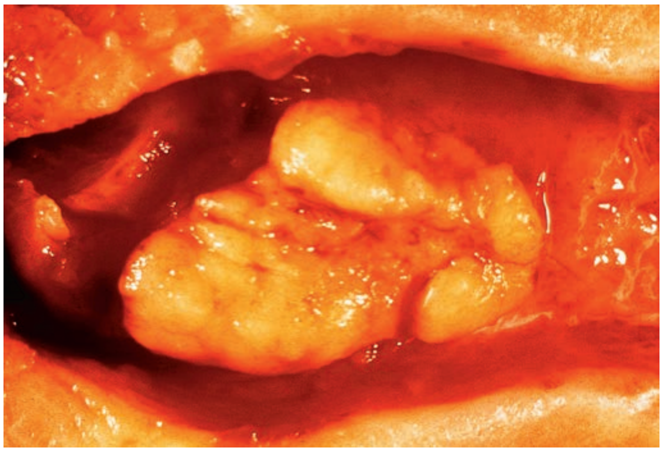


Figure 33.26 **Atypical Polypoid Adenomyoma.** The gross appearance is not substantially different from that of an ordinary polyp.

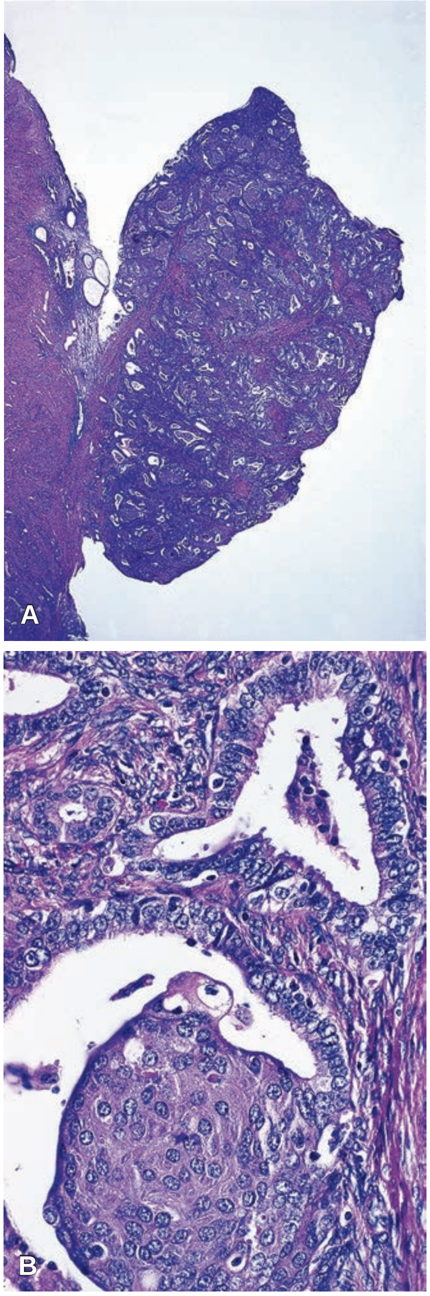


Figure 33.27 **A** and **B,** Whole-mount and high-power appearance of atypical polypoid adenomyoma. Note the glandular architectural complexity, metaplastic changes, and atypia.

Bokhman proposed that endometrial carcinoma be divided into two types, type I and type II, on the basis of their pathogenesis: one—by far the more common—occurring as a result of excess estrogenic stimulation and developing against a background of endometrial hyperplasia, and the other developing de novo, independent of estrogen stimulation, in older women.[217–219] The prototype for type I endometrial carcinoma is low-grade endometrioid carcinoma, while the prototype for type II endometrial carcinoma is serous carcinoma.

Patients at high risk for the first category include the obese, diabetic, hypertensive, and infertile; those with failure of ovulation (including PCOS) and dysfunctional bleeding; longstanding estrogen users; breast cancer patients treated with tamoxifen (see later); those with severe degrees of endometrial hyperplasia; and—to a much lesser degree—those with functioning granulosa cell tumors and thecomas.[220–222] Tumors in this category are typically low grade and the prognosis is favorable; treatment with progestins is an option, especially if preservation of fertility is desired.

There are no well-defined risk factors for patients with type II carcinomas. Occasional cases have been reported in patients with BRCA germline mutations,[215] but this is uncommon and certainly much less frequently encountered than with high-grade serous carcinoma of tubo-ovarian origin.[223] The prognosis of patients with type II carcinomas is much worse than that of patients with type I carcinomas.

The Cancer Genome Atlas (TCGA) study of 373 endometrial carcinomas opened important new windows onto the molecular subclassification of endometrial carcinoma.[223] As well as confirming the presence of type I and type II subtypes, which are characterized by low numbers of somatic copy number alterations (CN low)/wild-type expression pattern of p53, and high numbers of somatic copy number alterations in the genome (CN high)/abnormal expression of p53, respectively, two additional endometrial carcinoma molecular subtypes were identified, based on their mutation profiles: hypermutated endometrial carcinomas and ultramutated endometrial carcinomas. Together these latter two subtypes account for approximately one-third of endometrial carcinomas. The clinical significance of identification of these subtypes is still being explored but could prove to be dramatic, impacting on surgical and adjuvant treatment decisions.[224-232]

Hypermutated endometrial carcinomas are characterized by microsatellite instability (MSI) secondary to dysfunction of one of the enzymes that repairs DNA sequence abnormalities by the post-replicative DNA mismatch repair pathway. A surrogate test for identification of tumors in this category is immunohistochemistry for mismatch repair enzymes (MLH1, PMS2, MSH2, MSH6), which is increasingly preferred to MSI testing (Fig. 33.28). Because of dimerization of MMR proteins, screening for MMR deficiency (MMR-D) can be done by immunostaining for just two of the proteins, MSH6 and PMS2; if both are expressed the tumor is MMR intact. 3%–4% of endometrial carcinomas arise in patients with Lynch syndrome, and these tumors are MMR-D. The endometrial carcinomas in Lynch syndrome patients often present at a young age.[233–235] MMR-D endometrial carcinomas tend to be higher grade and associated with peritumoral and intratumoral lymphocytic infiltrates.[233,234] Although most are endometrioid, they may be nonendometrioid histology.[233] Most MMR-D endometrial carcinomas are not associated with Lynch syndrome; the MMR-D phenotype in these cases is secondary to somatic events, most commonly promoter methylation of *MLH1*, with loss of protein expression. Compared to MMR-D endometrial carcinomas in patients with Lynch syndrome, those with somatic *MLH1* promoter methylation arise in older patients and are more likely to be endometrioid type, show mucinous differentiation, and have tumor infiltrating lymphocytes.[236]

Ultramutated endometrial carcinomas have 10-fold more mutations than the hypermutated tumors, and the molecular basis for this is mutations, almost invariably somatic, in the polymerase-epsilon (POLE) gene, resulting in loss of the exonuclease proofreading function and increased mutation rates. The tumors associated with POLE exonuclease domain mutations (POLE EDMs) are associated with a very favorable prognosis, even though they are often higher grade.[224–226,237] They are typically of endometrioid histotype and, like the MMR-D tumors, are commonly associated with prominent lymphoid infiltrates (Fig. 33.29).[227]

The clinical, molecular, and pathologic features associated with each of the major molecular subtypes of endometrial carcinoma (type I/CN low/p53 wildtype, type II/CN high/p53 abn, MMR-D, POLE EDM) are summarized in Table 33.1, and the differences in prognosis are shown in Figure 33.30. The conventional histopathologic features of endometrial carcinoma, such as grade and histotype, correlate imperfectly with the molecular subtypes, so for the foreseeable future we will include these findings in our pathology reports. Accordingly, the remainder of this section will focus on the histopathologic assessment of endometrial carcinoma.

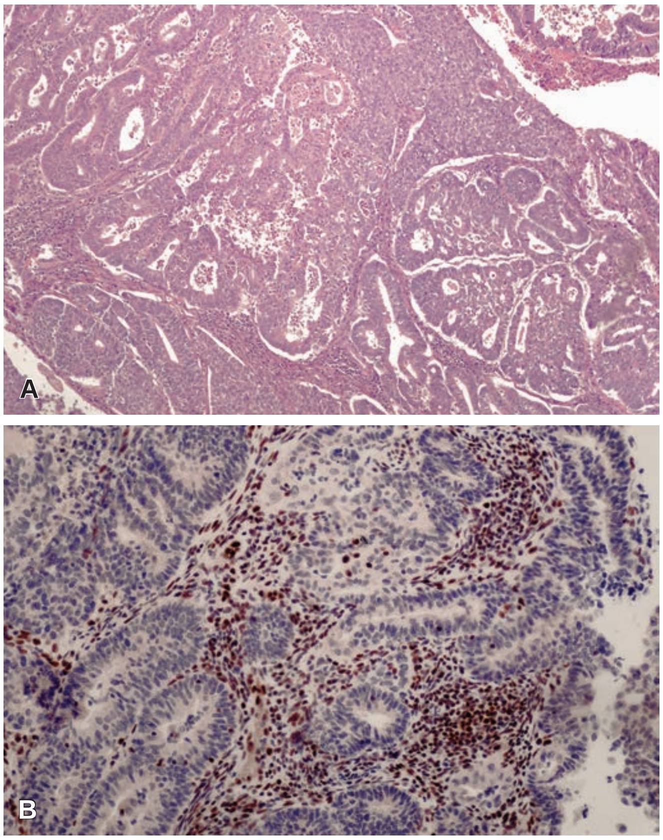


Figure 33.28 Hypermutated/Mismatch Repair Deficient Endometrial Carcinoma. There is heterogeneity in the appearance of the tumor, with more solid areas alternating with glandular areas (**A**) and a prominent lymphoid infiltrate. Immunostaining shows loss of expression of MLH1 in the tumor cells, with retained expression in lymphocytes and stromal cells (**B**).

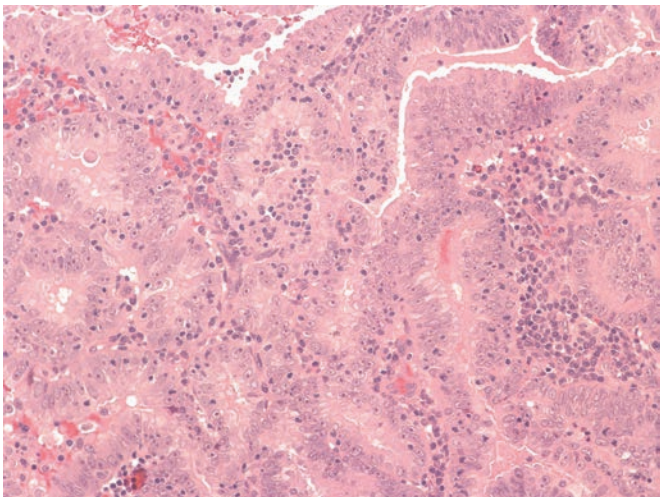


Figure 33.29 Ultramutated/Polymerase Epsilon Exonuclease Domain Mutated (POLE EDM) Endometrial Carcinoma. The cells of this endometrioid carcinoma show high-grade nuclear features, and there is a prominent lymphoid infiltrate, features associated with POLE EDM tumors.

Table 33.1 Genomic-based endometrial carcinoma subtypes

TCGA CATEGORY[223]	GENOMIC ALTERATION	SURROGATE MARKER	FORMER DESIGNATION[229]	AGE[217]	PROGNOSIS	HISTOTYPE
CN low	Few mutations, low # of somatic copy number alterations	Absence of POLE EDM, MMR-D and p53 abn	Type I	65 years	Intermediate	Endometrioid (usually grade 1 or 2)
CN high	Few mutations, low # of somatic copy number alterations	p53 abn	Type II	72 years	Poor	Serous and some grade 3 endometrioid
Hypermutated	Many mutations	MMR-D	NA	66 years	Intermediate	Mostly endometrioid, may be high grade
Ultramutated	Very many mutations	POLE EDM	NA	62 years	Favorable	Endometrioid, may be high grade

CN high, High numbers of somatic copy number abnormalities; *CN low*, low numbers of somatic copy number abnormalities; *MMR-D*, mismatch repair deficient; *NA*, not applicable; *p53 abn*, abnormal p53 expression by immunohistochemistry that is either complete absence of expression or strong diffuse overexpression; *POLE EDM*, mutations in the POLE exonuclease domain; *TCGA*, The Cancer Genome Atlas.

Pathologic Features

Grossly, carcinoma of the endometrium may form broad-based polypoid masses or infiltrate diffusely into the myometrium (Fig. 33.31). In general, extensive myometrial invasion is accompanied by clinically detectable uterine enlargement. However, notable exceptions occur; sometimes deep myometrial extension is accompanied by a normal-sized uterus, the pattern of growth resembling that of adenoma malignum of cervix.[223]

Endometrial carcinoma can develop in any anatomic region of the mucosa. Tumors developing in younger women have a greater tendency to involve the lower uterine segment (isthmus).[238] Most tumors thought to have arisen in the isthmus are best included among the endometrial rather than the cervical carcinomas, based on the clinical and biomarker expression profiles.[239] Small carcinomas restricted to a cornu can be missed by a biopsy or D&C.

Microscopically, approximately 80% of endometrial malignant epithelial tumors are conventional adenocarcinomas, which are usually divided into well (grade 1, 50%), moderately (grade 2, 35%), and poorly differentiated (grade 3, 15%) tumors (Fig. 33.32A–C). The FIGO three-grade system is primarily based on the growth pattern (relative proportion of glandular and solid areas), with grade 1 having 5% or less solid growth, grade 2 5%–50% solid growth, and grade 3 >50% solid growth, but it also makes provisions for nuclear atypia, with grade increased by one in the presence of notable nuclear atypia, defined as grade 3 nuclei in more than 50% of the tumor.[223,240] Because there are minimal prognostic differences between grade 1 and grade 2, and they are treated identically with respect to adjuvant chemotherapy and radiation therapy, it has also been proposed that grade 1 and 2 be combined as "low grade."

The better differentiated tumors closely recapitulate the light and electron microscopic features of the non-neoplastic endometrium,[241,242] hence the term "endometrioid" that is used for them. Over one-fourth of the endometrioid carcinomas have papillary (villoglandular) foci, either on the surface or in the invasive areas (see Fig. 33.32D).[243] These tumors should be sharply separated from the much more aggressive serous carcinomas.[244–246] A further variation on the theme is represented by endometrioid adenocarcinomas containing small nonvillous papillae. These papillae can arise either from an otherwise unremarkable endometrioid carcinoma or from the villous projections of the villoglandular variant of this tumor.[247] It should also be noted that the most superficial portions of endometrial adenocarcinomas can exhibit patterns closely simulating various hyperplastic and metaplastic conditions of the endometrial mucosa.[248]

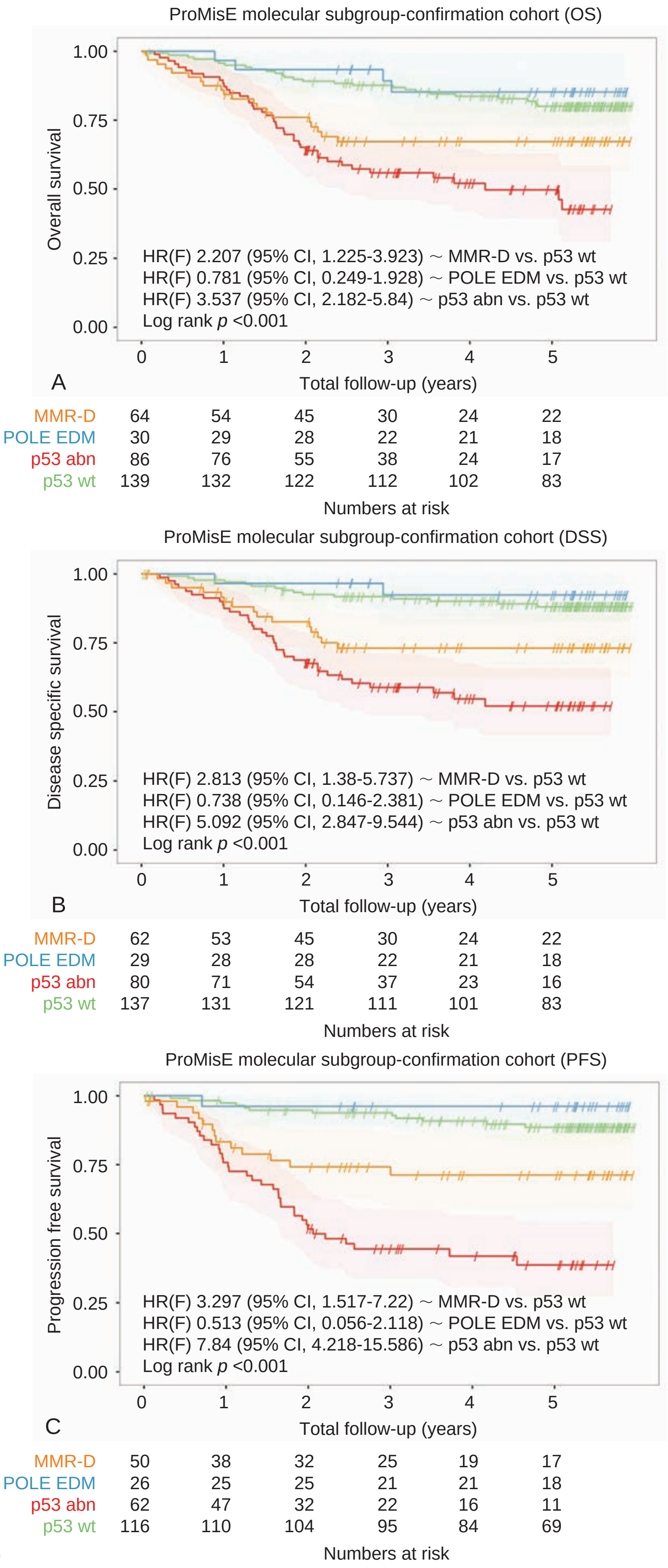
The stroma of endometrial adenocarcinoma may contain collections of foamy cells, probably the result of tumor necrosis.[249] However, these cells can also be seen in hyperplasia and in the absence of proliferative epithelial changes. Their immunophenotype corresponds to that of histiocytes rather than endometrial stromal cells.[250]

The non-neoplastic endometrium of a uterus harboring an endometrioid adenocarcinoma is often hyperplastic and only exceptionally exhibits a normal secretory pattern.[251]

The frequency and extent of myometrial invasion by carcinoma correlate with the microscopic grade of the tumor.[187] High-grade tumors are significantly associated with cervical involvement and lymphovascular invasion.[253] Care should be exercised to distinguish true myometrial extension by carcinoma from expansion of the endometrial–myometrial junction and from atypical or malignant changes involving preexisting foci of adenomyosis[254]; the latter condition is recognized by the presence of endometrial stroma around the intramyometrial proliferating glandular foci.[255] It has been proposed that CD10 immunostaining can help in this distinction by highlighting the endometrial stroma associated with the adenomyosis when present.[256] However, a warning has been sounded to the effect that CD10 immunoreactivity can also be found around foci of invasive adenocarcinoma,[257] and we do not recommend immunostaining in the assessment of myometrial invasion. If there is doubt about the presence of myometrial invasion, it can be communicated in the surgical pathology report by indicating that "no definite myometrial invasion" is identified.

Extension of the endometrial carcinoma into the cervix occurs in over 10% of cases, usually by direct invasion,[258,259] but can also be discontinuous with the endometrial tumor (presumably by mucosal "drop" implantation or via lymphatic spread). This extension may be grossly evident or become apparent only on microscopic examination. It is important, for staging purposes, to distinguish between surface/mucosal involvement only, which does not impact on stage, and invasion of the cervical stroma, which does result in a tumor being stage II.[223,259] Assessment of cervical stromal invasion is challenging, and there is considerable interobserver variability in assessment of this important feature and, consequently, tumor stage.[260]

With respect to the molecular subtype of endometrioid carcinomas, the low-grade (grade 1 or grade 2) tumors consist of type I/CN low/p53 wild type, MMR-D and POLE mutant tumors, while high-grade



ProMisE molecular subgroup-confirmation cohort (OS)

HR(F) 2.207 (95% CI, 1.225-3.923) ~ MMR-D vs. p53 wt
HR(F) 0.781 (95% CI, 0.249-1.928) ~ POLE EDM vs. p53 wt
HR(F) 3.537 (95% CI, 2.182-5.84) ~ p53 abn vs. p53 wt
Log rank *p* <0.001

	0	1	2	3	4	5
MMR-D	64	54	45	30	24	22
POLE EDM	30	29	28	22	21	18
p53 abn	86	76	55	38	24	17
p53 wt	139	132	122	112	102	83

Numbers at risk

ProMisE molecular subgroup-confirmation cohort (DSS)

HR(F) 2.813 (95% CI, 1.38-5.737) ~ MMR-D vs. p53 wt
HR(F) 0.738 (95% CI, 0.146-2.381) ~ POLE EDM vs. p53 wt
HR(F) 5.092 (95% CI, 2.847-9.544) ~ p53 abn vs. p53 wt
Log rank *p* <0.001

	0	1	2	3	4	5
MMR-D	62	53	45	30	24	22
POLE EDM	29	28	28	22	21	18
p53 abn	80	71	54	37	23	16
p53 wt	137	131	121	111	101	83

Numbers at risk

ProMisE molecular subgroup-confirmation cohort (PFS)

HR(F) 3.297 (95% CI, 1.517-7.22) ~ MMR-D vs. p53 wt
HR(F) 0.513 (95% CI, 0.056-2.118) ~ POLE EDM vs. p53 wt
HR(F) 7.84 (95% CI, 4.218-15.586) ~ p53 abn vs. p53 wt
Log rank *p* <0.001

	0	1	2	3	4	5
MMR-D	50	38	32	25	19	17
POLE EDM	26	25	25	21	21	18
p53 abn	62	47	32	22	16	11
p53 wt	116	110	104	95	84	69

Numbers at risk

Figure 33.30 Outcomes of patients with the four genomic subtypes of endometrial carcinoma (POLE exonuclease domain mutation [POLE EDM], CN low/p53 wildtype, mismatch repair deficient [MMR-D], and CN high/p53 abnormal, from best to worst prognosis). **A,** Overall survival. **B,** Disease-specific survival. **C,** Progression-free survival. (From Talhouk A, McConechy MK, Leung S, et al. Confirmation of ProMisE: A simple genomics-based classifier for endometrial cancer. *Cancer* 2017;123:802–813.)

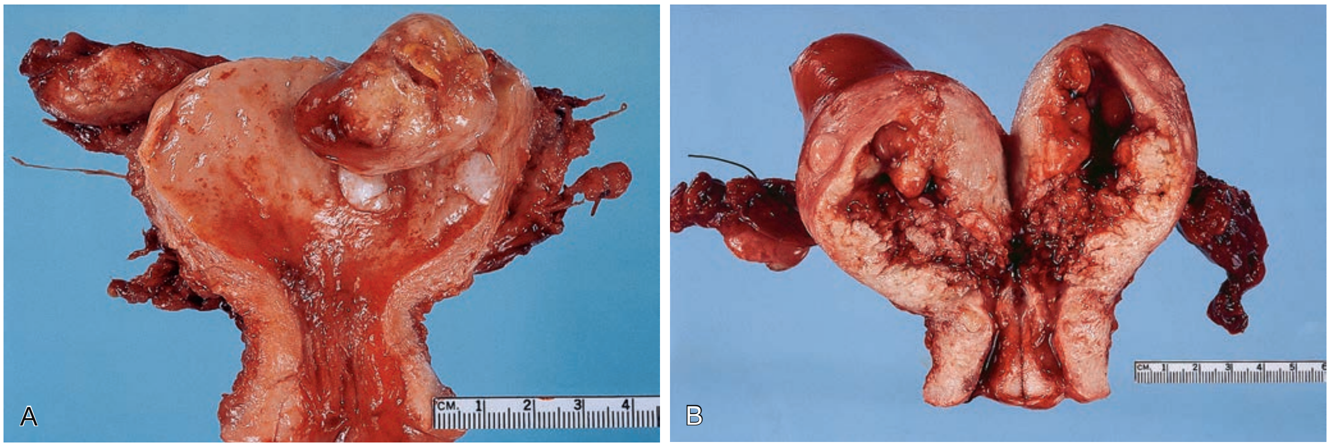


Figure 33.31 **A** and **B,** Gross appearances of endometrioid adenocarcinoma. The tumor shown in **A** is polypoid, whereas that depicted in **B** is highly infiltrating.

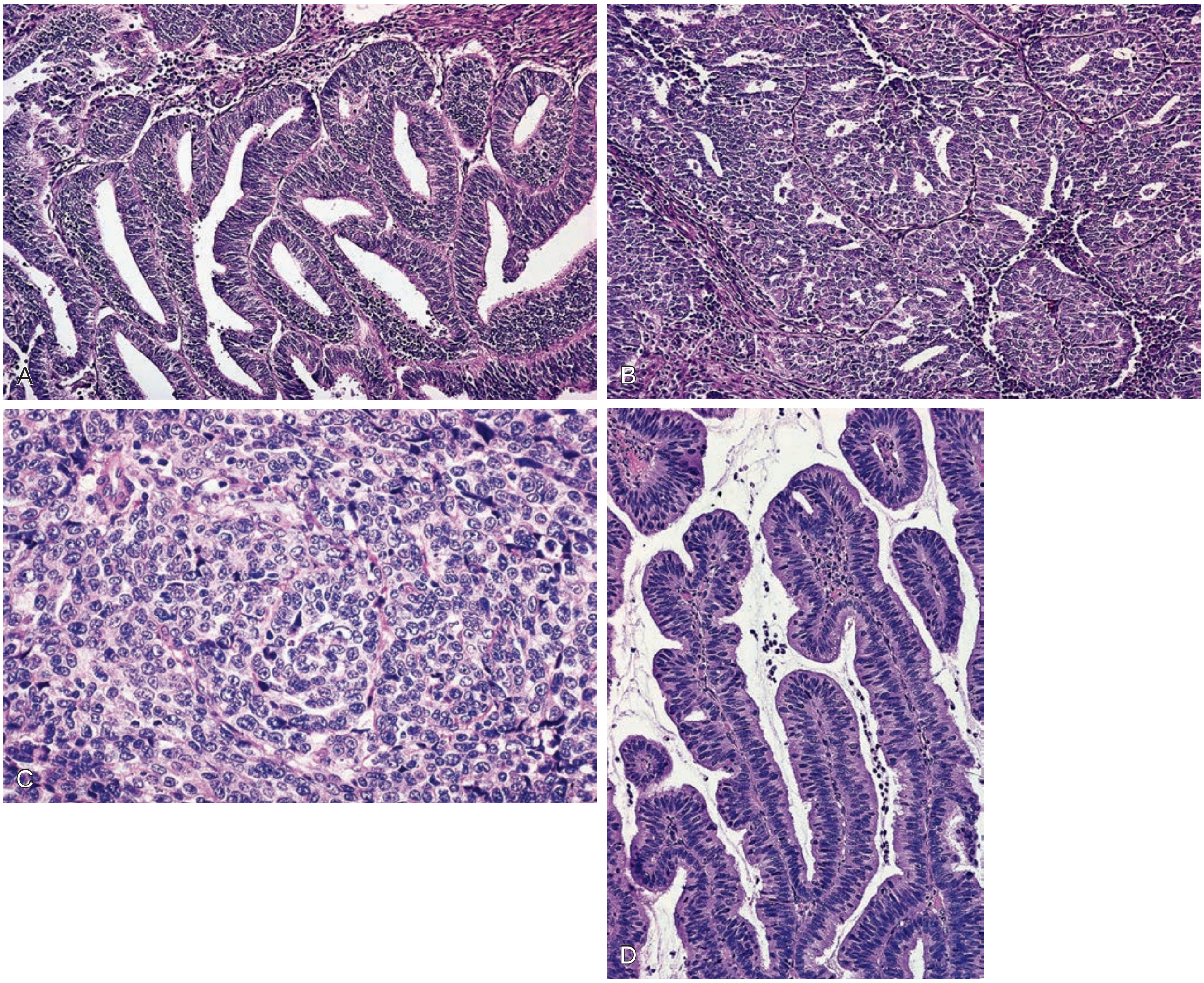


Figure 33.32 **Endometrioid Endometrial Adenocarcinoma. A,** Grade 1; **B,** grade 2; **C,** grade 3; **D,** with villoglandular pattern of growth.

(grade 3) endometrioid carcinomas can be any of the four molecular subtypes.

The differential diagnosis between endometrial and endocervical carcinoma is discussed elsewhere.

Variants of Endometrioid Carcinoma and Other Endometrial Carcinoma Histotypes

Numerous morphologic forms of endometrial adenocarcinoma have been described. Some, such as adenocarcinoma with squamous differentiation, mucinous carcinoma, and secretory carcinoma, are thought to represent variants of ordinary ("endometrioid") adenocarcinoma. Others, notably serous carcinoma, carcinosarcoma, and clear cell carcinoma, are regarded as being of nonendometrioid type, although any of them can be seen coexisting with endometrioid adenocarcinoma.

Adenocarcinoma with squamous differentiation (formerly known as adenoacanthoma if low grade and adenosquamous carcinoma if high grade) refers to endometrioid adenocarcinoma containing squamous elements derived from metaplasia of the tumor glands (Figs. 33.33 and 33.34). Its natural history closely parallels that of the ordinary endometrioid adenocarcinoma of a similar degree of differentiation lacking squamous changes.[261] **Glassy cell carcinoma** is a variant of endometrioid carcinoma with squamous differentiation that has occasionally been reported in the endometrium; its appearance is similar to that of its more common cervical counterpart.[262,263]

Corded and hyalinized endometrioid carcinoma (CHEC) is characterized by epithelial cells in cords separated by hyalinized stroma. Spindled epithelial cells are also commonly encountered.[264] The nuclei are grade 1 or 2, which serves to separate these low-grade variants of endometrioid carcinoma with carcinosarcoma, with which they are often confused.

The **microcystic, elongated, and fragmented** (MELF) pattern of invasive endometrioid adenocarcinoma is recognized for its subtle histologic features that may be easily overlooked (particularly at the time of frozen section analysis for depth of myoinvasion) and its possible staging implications.[265] MELF is characterized by small pockets of a fibromyxoid stromal reaction that contain varying patterns of admixed eosinophilic carcinoma cells: small glands with attenuated epithelium (i.e. microcysts), elongated glands with a flattened lining mimicking endothelial cells, or clusters of detached cells or individual cells. Associated lymphocytes and neutrophils are common. Lymphovascular invasion in the myometrium and lymph node metastases are commonly identified, and often have a very subtle "histiocyte-like" appearance.[266–268] Data on the long-term clinical significance of this pattern of endometrial cancer are still emerging.

Secretory carcinoma is characterized by neoplastic glands having subnuclear vacuolization resembling that of a normal 17-day secretory

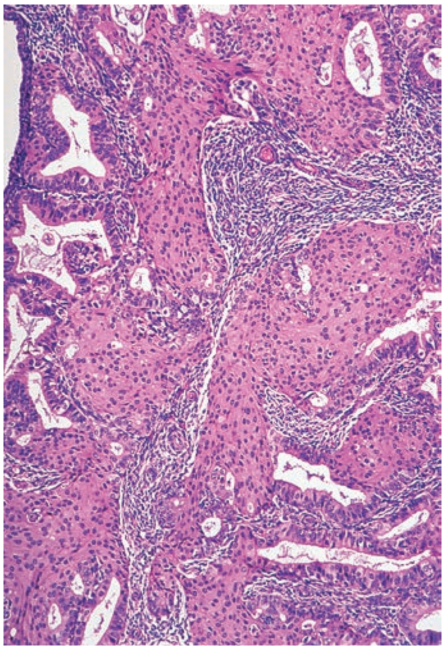


Figure 33.33 Well-differentiated endometrioid adenocarcinoma with squamous metaplasia.

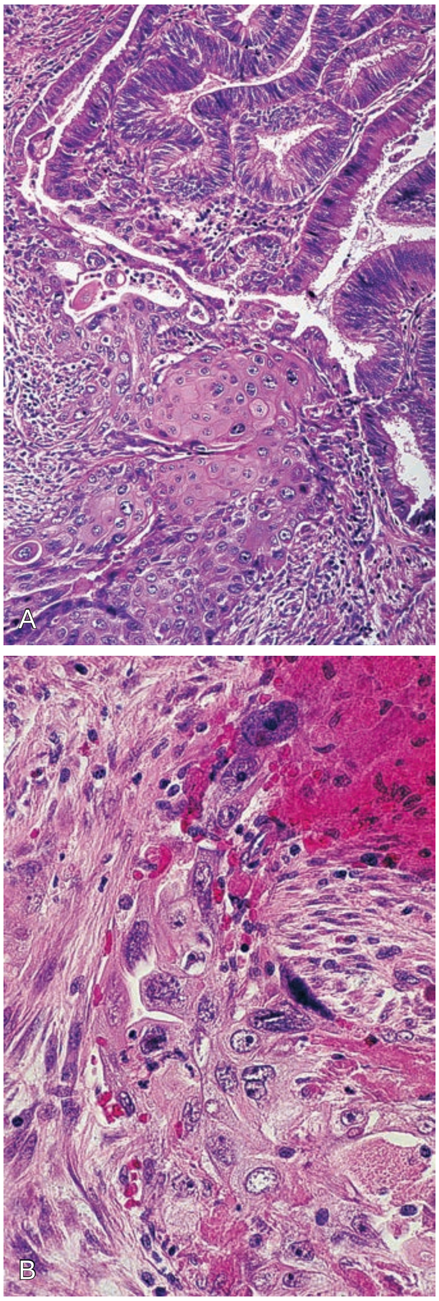


Figure 33.34 **A** and **B,** Endometrial adenocarcinoma of endometrioid type with squamous metaplasia. In contrast to the case shown in Fig. 33.36, the squamous component has markedly atypical cytologic features.

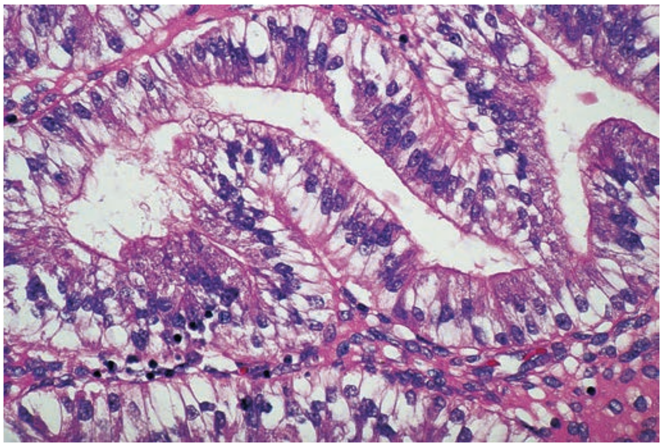


Figure 33.35 Secretory Carcinoma of Endometrium. This well-differentiated lesion is a variant of endometrioid adenocarcinoma and is composed of cells with abundant clear to finely granular cytoplasm. It should be distinguished from clear cell carcinoma.

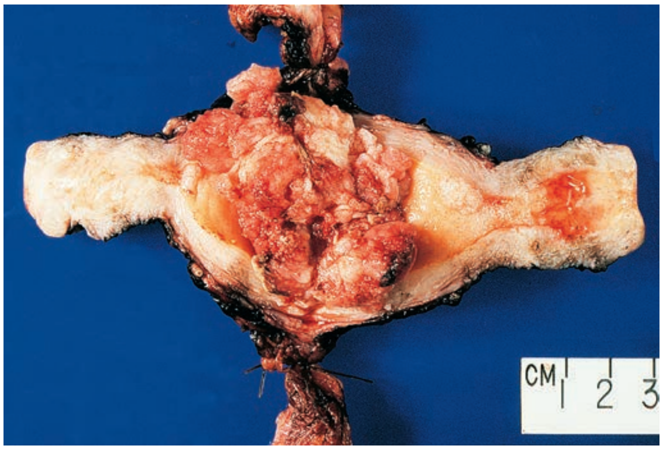


Figure 33.36 Gross appearance of serous carcinoma of endometrium. The neoplasm fills the endometrial cavity.

endometrium and accompanied by a late secretory pattern in the adjacent noninvolved endometrium (Fig. 33.35).[269] This tumor is believed to be the expression of a pattern that may be present diffusely or focally in a well-differentiated endometrioid carcinoma, usually as a result of progesterone stimulation. It should be distinguished from clear cell carcinoma, described later.[270–272]

Mucinous adenocarcinoma is a tumor subtype characterized by abundant intracellular mucin within the tumor cells.[273] Areas of mucinous differentiation are relatively common in usual endometrioid adenocarcinoma and is not of clinical significance. By definition, mucinous adenocarcinoma must consist predominantly (i.e. >50%) of tumor cells showing mucinous differentiation, and when so defined, this is a rare variant of endometrial adenocarcinoma. It is distinguished from atypical mucinous glandular proliferation of the endometrium (the mucinous equivalent of atypical hyperplasia) by increased glandular architectural complexity. Cytologic atypia is of limited help in this differential diagnosis as it is often minimal, even in mucinous carcinoma. There is often a prominent neutrophilic infiltrate in the epithelium of mucinous carcinoma of the endometrium. The distinction between endometrial mucinous adenocarcinoma and primary endocervical adenocarcinoma can be made based on immunostains, with the former showing strong diffuse ER and PR positivity, in most instances, and lacking block p16 positivity, while cervical mucinous carcinomas show block p16 positivity if HPV-associated, or are ER/PR negative if HPV-independent adenocarcinomas of gastric type.[274,275] On occasion, endometrial adenocarcinomas of mucinous or mixed mucinous–endometrioid type exhibit a conspicuous *microglandular* pattern associated with eosinophilic mucinous intraluminal secretion and prominent acute inflammation, the overall picture simulating the appearance of endocervical microglandular hyperplasia.[276,277]

Serous carcinoma is a highly aggressive form of endometrial adenocarcinoma closely resembling tubo-ovarian high-grade serous carcinoma (Fig. 33.36).[278-280] It is characterized by a complex papillary pattern of growth, a high degree of cytologic atypia (pleomorphism, hyperchromasia, giant nucleoli), numerous mitoses, extensive necrosis, psammoma bodies (30% of the cases), and prominent myometrial invasion (Fig. 33.37). It should be distinguished from the already mentioned (and much more common) endometrial adenocarcinoma with a villoglandular pattern of growth, with which it shares several architectural features.[281] A key aspect in this regard is the consistently high-grade nature of its cytologic features.[282] Conversely, papillae

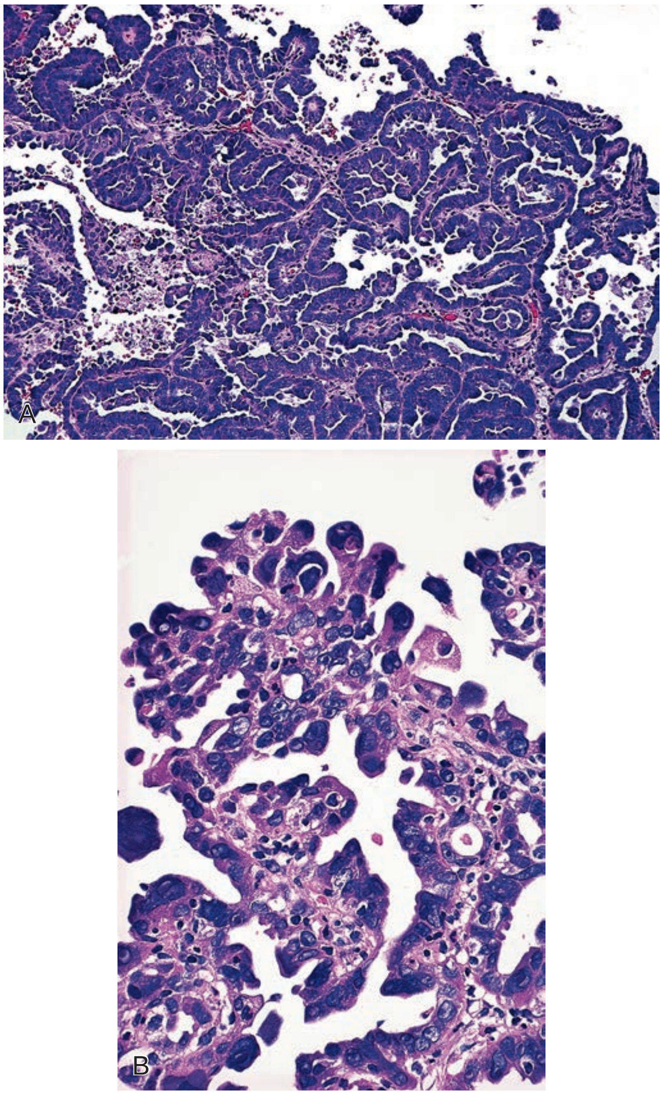


Figure 33.37 **A** and **B,** Low- and high-power appearance of serous carcinoma. Note the high nuclear grade.

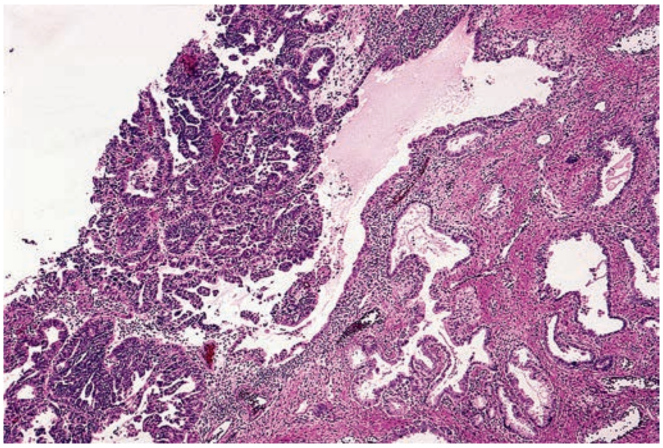


Figure 33.38 Serous carcinoma limited to the superficial portion of an endometrial polyp.

may be scanty, the tumor growing predominantly in the form of tubuloglandular structures with angulated outlines and compressed lumens, raising a differential diagnosis with endometrioid carcinoma.[283] The glandular luminal margin in serous carcinoma with glandular differentiation appears ragged, in contrast to the smooth margin typical of endometrioid adenocarcinoma. It should be mentioned here that psammoma bodies are not necessarily indicative of a serous-type tumor, since occasionally they are also seen in endometrioid carcinomas.[241]

Uterine serous carcinoma can coexist with endometrioid adenocarcinoma of the uterus,[284] be confined to an endometrial polyp, or be entirely intramucosal ("minimal serous carcinoma") (Fig. 33.38).[242,284–291] Even when confined to a polyp there can occasionally be extra-uterine spread, presumably by a transtubal route.[292,293] A putative precursor of serous carcinoma has been described under the term *endometrial glandular dysplasia*.[277,294,295] In patients with widespread involvement by high-grade serous carcinoma in which there is endometrial involvement, most such tumors are endometrial primary tumors.[292] WT1 is less commonly positive in endometrial serous carcinoma than in tubo-ovarian serous carcinoma, but it is not a reliable marker in an individual case. When there is extensive serous carcinoma with significant endometrial involvement, it is our practice to stage it as an endometrial primary tumor and not do immunostains.[293]

Immunohistochemically, abnormal immunostaining for p53 (either strong and diffuse staining or complete absence of staining) is characteristic of serous carcinoma, although not every serous carcinoma will show abnormal p53 staining, and approximately 30% of high-grade endometrioid carcinomas show abnormal p53 immunoreactivity. Thus staining for p53 does not help in distinguishing between serous carcinoma and high-grade endometrioid carcinoma, but it can be useful in cases of glandular tumors with greater atypia than is expected for a low-grade endometrioid carcinoma, but lacking unequivocal high-grade cytologic features of serous carcinoma. Abnormal p53 immunostaining in these so-called "ambiguous" cases supports a diagnosis of serous carcinoma.[296] By molecular classification, the serous carcinomas are almost all type II/CN high/p53 abn subtype.

Carcinosarcoma (formerly referred to as malignant mixed müllerian tumor) was for many years considered to be a variant of uterine sarcoma but is now, based on a number of lines of evidence, classified as an endometrial carcinoma with metaplastic sarcomatous differentiation. Carcinosarcomas are practically always seen in postmenopausal patients, although exceptions occur.[297] Grossly, they present as large, soft, polypoid growths involving the endometrium and myometrium, sometimes protruding from the cervix (Fig. 33.39). Foci of necrosis and hemorrhage are common.

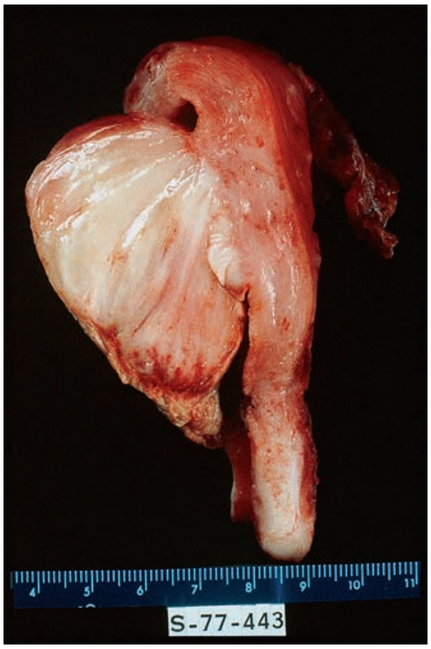


Figure 33.39 Carcinosarcoma of uterus resulting in a huge polypoid mass.

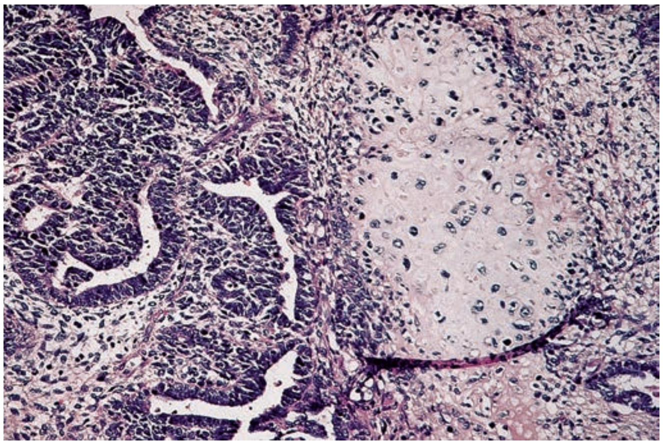


Figure 33.40 Glandular and mesenchymal components of carcinosarcoma. Heterologous elements in the form of cartilage are present.

Microscopically, the distinctive feature of carcinosarcomas is the *admixture of carcinomatous and sarcoma-like elements*, resulting in a characteristic biphasic appearance (Fig. 33.40). The transition between carcinoma and sarcoma should be abrupt; if it is not, consider one of the mimics of carcinosarcoma, such as dedifferentiated carcinoma or endometrioid carcinoma with corded and hyalinized (CHEC) pattern. The carcinomatous component is usually of glandular type, whether endometrioid, clear cell, or papillary serous (particularly the latter).[298] As a rule, it has a poorly differentiated appearance and is of a high-grade nature; therefore, a careful search for sarcomatous elements should be carried out whenever such patterns are found in an endometrial biopsy, particularly if accompanied by extensive necrosis and hemorrhage. Squamous cell, undifferentiated, and primitive neuroectodermal patterns may also be seen.[299,300] Cases have also been described with melanocytic[301] and yolk sac differentiation.[302]

The appearance of the sarcomatous component is the basis for the time-honored division of these neoplasms into a *homologous* and a *heterologous* variety. In the former, the malignant stroma is composed either of round cells resembling those of the endometrial stroma or of spindle cells resembling leiomyosarcoma or fibrosarcoma. In the latter, specific heterologous mesenchymal elements (such as skeletal muscle, cartilage, bone, or adipose tissue) are also present (see Fig. 33.40). Identification of cross striations, or of skeletal muscle markers by immunocytochemistry (e.g. myogenin), is required to document the presence of a rhabdomyosarcomatous component. In some cases this component is so prominent as to overgrow the epithelial elements and to mimic a pure rhabdomyosarcoma.[281] Conversely, the sarcoma-like component may be very inconspicuous. The metastases are most commonly purely epithelial but may be mixed or purely sarcomatous. Exceptionally, a rhabdoid component is present.[303]

Keratin expression is always detectable in the epithelial areas but is also present, albeit reduced, in the sarcomatous component in most cases.[304] Carcinosarcomas can show genetic changes of a type I endometrial carcinoma with progression (i.e. both *PTEN* and/or *ARID1A* mutations AND mutation in *TP53*), or those of a type II endometrial carcinoma (*TP53* mutations without *PTEN* or *ARID1A* mutations), and carcinosarcoma may be an end result of tumor progression in both pathways.[305] Carcinosarcomas are rare among the hypermutated/MMR-D or ultramutated/POLE mutant tumors but there is relatively little data available regarding this point at the time of writing.

Carcinosarcomas are easily distinguished from teratomas by their occurrence in an older age group and by the absence of skin appendages, glia, thyroid, and other tissues; however, as already noted, they may exceptionally contain neuroectodermal elements.[299] They should also be clearly separated from embryonal rhabdomyosarcoma (sarcoma botryoides). The latter term should be reserved for the tumor of childhood or adolescence arising from the cervix or vagina that exhibits skeletal muscle differentiation but lacks a carcinomatous component.

Carcinosarcomas are highly aggressive neoplasms, perhaps more so than even the higher grades and the more unfavorable histotypes of endometrial carcinoma.[306] Extension into the pelvis, lymphatic and vascular permeation, and distant lymph-borne and blood-borne metastases are all common. If the tumor has extended to the serosa of the uterus or beyond at the time of surgery, the prognosis is very poor. In several series, tumors having only homologous stromal elements have been found to have a better prognosis than those with heterologous elements.[307–310] It should be pointed out, however, that the difference between the two is generally small, in some series absent altogether, and far outweighed by the stage of the disease.[311–313]

Carcinosarcomas are the most common uterine tumors to arise in the uterus after irradiation, typically for cervical carcinoma; these postirradiation tumors start to appear 8–10 years after radiation therapy and are associated with a particularly poor prognosis.[314,315]

Clear cell carcinoma is composed of large clear cells with distinct cellular margins containing variable but usually large amounts of glycogen (Figs. 33.41 and 33.42).[271,316] The papillary formations and "hobnail" cells found in this variant of adenocarcinoma resemble those seen in the ovarian, cervical, and vaginal tumors that carry the same name. The ultrastructural and immunohistochemical features of this tumor support their being of müllerian origin, and not mesonephric as was originally believed.[317–320] Most patients are postmenopausal.

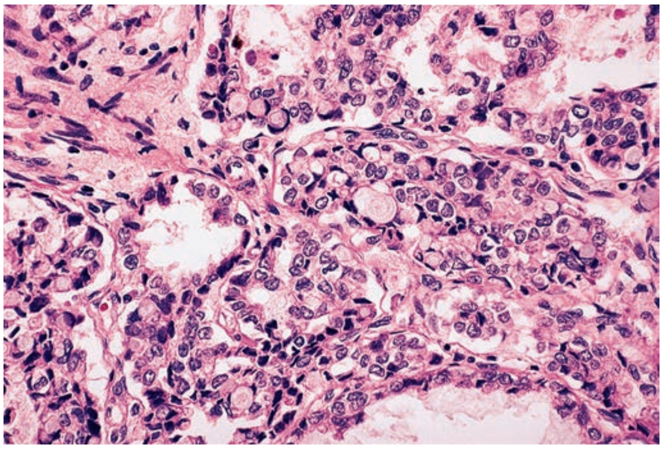


Figure 33.41 Clear cell carcinoma of endometrium.

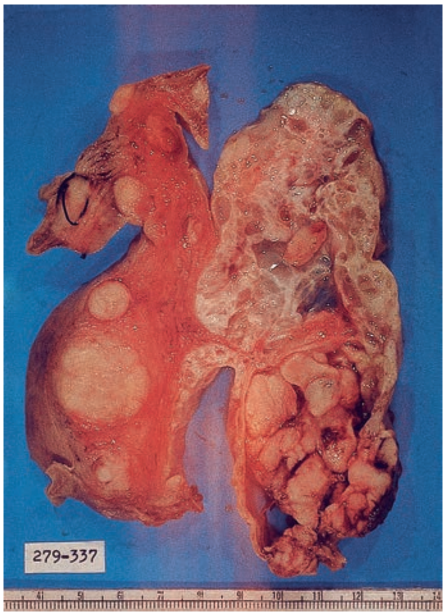


Figure 33.42 Gross appearance of a clear cell carcinoma involving a large endometrial polyp. (Courtesy Dr. Juan José Segura, San José, Costa Rica.)

A rare variant of clear cell carcinoma is characterized by a predominant or exclusive component of large eosinophilic (oxyphilic) cells.[321] Unlike serous carcinomas, most clear cell carcinomas express p53 in a wild type pattern. They are typically negative for ER and PR expression. A putative precursor lesion has been described, characterized by endometrial cells with clear and/or eosinophilic cytoplasm and varying degrees of nuclear atypia.[322]

Undifferentiated carcinoma and the closely related **dedifferentiated carcinoma**, where there is a component of low-grade endometrioid carcinoma present,[323] have emerged as a distinct entity. It grows in the form of solid sheets of cells without any signs of differentiation (Fig. 33.43).[323,324] Epithelial differentiation is inconspicuous and the differential diagnosis may include sarcoma or hematopoietic malignancy. It is important to distinguish it from a grade 3 endometrioid adenocarcinoma because of its worse prognosis.[325] Some of the reported cases of undifferentiated carcinoma have occurred in young women and have pursued a fulminant clinical course.[326] Undifferentiated and dedifferentiated carcinoma are characterized by mutations in genes in the SWI/SNF chromatin

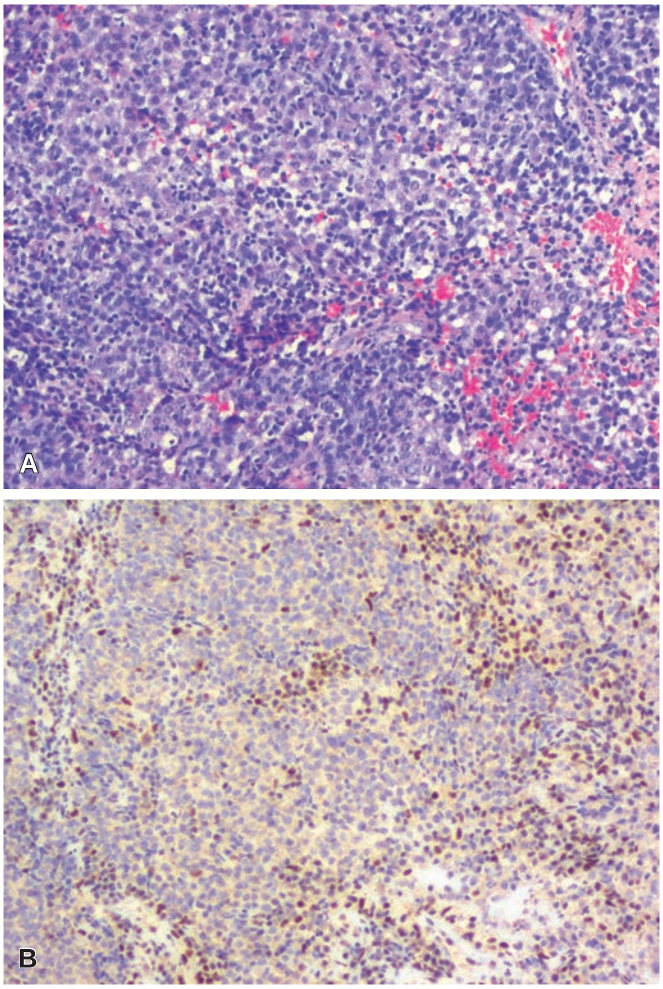


Figure 33.43 Undifferentiated carcinoma (**A**), with loss of MLH1 expression in the tumor cells (**B**).

remodeling complex (the same gene family mutated in ovarian small cell carcinoma of hypercalcemic type) and they typically show weak/focal expression of keratins, loss of PAX8 expression and wild type p53 expression, with frequent loss of expression of mismatch repair proteins (see Fig. 33.43B).[327–329]

Small cell (neuroendocrine) carcinoma usually presents grossly as bulky (sometimes polypoid), ill-defined, and invasive tumor. In rare instances it is seen confined to an endometrial polyp.[330] Microscopically, its appearance is similar to that of its more common cervical counterpart. It may be associated with areas of ordinary endometrioid or serous adenocarcinoma or be seen as a component of carcinosarcoma.[331–333] Immunohistochemically, there is usually reactivity for neuron-specific enolase (NSE) and low-molecular-weight keratin and sometimes also for chromogranin and synaptophysin. Dense-core secretory granules can be detected ultrastructurally. The behavior is very aggressive.[334] As in the lung, cervix, and other sites, tumors with similar high-grade neuroendocrine features but composed of cells of intermediate or large size exist, either pure or admixed with endometrioid adenocarcinoma.[324,335] In this context, it should be noted that a minor population of endocrine cells—as detected with argyrophilic stains—is present in 25%–50% of otherwise typical endometrial adenocarcinomas.[336,337] Some of these cells have been found to contain chromogranin, NSE, 5-hydroxytryptamine (5-HT; serotonin), somatostatin, adrenocorticotropic hormone (ACTH), and indolamines.[338,339]

Squamous cell carcinoma occurring in the endometrium in a pure form is extremely rare,[340,341] and it is, therefore, particularly important to rule out the alternative possibility of extension of a cervical carcinoma.[342] Some cases have developed in elderly patients with pyometra, presumably on the basis of a preexisting endometrial squamous metaplasia.[343] One reported case was associated with *spindle cell (sarcomatoid)* changes,[344] and another was of the *verrucous type*.[345]

Giant cell carcinoma is a rare pleomorphic form of high-grade endometrial adenocarcinoma featuring poorly cohesive sheets and nests of bizarre multinucleated giant cells.[346,347] It may be combined with better differentiated areas showing endometrioid or clear cell carcinoma features.[347]

Endometrial carcinoma with trophoblastic (choriocarcinomatous) or yolk sac differentiation should be distinguished from the giant cell carcinoma (just described), as well as malignant germ tumor, and gestational choriocarcinoma.[348] The multinucleated syncytiotrophoblast-like cells present in the choriocarcinomatous differentiation are strongly immunoreactive for human chorionic gonadotropin (hCG), while yolk sac differentiation is associated with expression of alpha-fetoprotein.[349–351] The conventional endometrial adenocarcinoma areas are more likely to have a serous than an endometrioid morphology.

Endometrioid carcinoma with sertoliform (sex cord–like) differentiation similar to that more commonly seen in ovarian endometrioid tumors has been reported.[352,353] This phenomenon is to be distinguished from the uterine tumors resembling ovarian sex-cord tumors (UTROSCTs). The term *corded and hyalinized endometrioid carcinoma* (so called CHEC pattern) is probably a variant of this sex cord–like differentiation, and it is important to distinguish it from carcinosarcoma, a more aggressive neoplasm.[264]

Hepatoid adenocarcinoma has been reported as arising from the endometrium, in association with alpha-fetoprotein production.[354]

Signet ring cell adenocarcinoma has been described as a primary uterine tumor.[355] Before making this diagnosis, all attempts should be made to rule out the alternative possibilities of metastasis (particularly from breast and stomach) and of vacuolated decidual cells and stromal histiocytes simulating signet ring cells.[356]

Lymphoepithelioma-like carcinoma looks like its homonym in other sites. The few reported cases have not shown evidence of Epstein–Barr virus infection.[357]

Rhabdoid tumor of the uterus represents, in at least some of the cases, a dedifferentiated form of endometrial adenocarcinoma, as is strongly suggested by its occasional coexistence with a conventional adenocarcinoma appearance.[358]

Mesonephric (adeno)carcinoma of the endometrium, that is, a tumor truly derived from wolffian remnants and, therefore, unrelated to the clear cell carcinoma described earlier (which in the past was inaccurately called mesonephric), has been described, presenting as a myometrial mass.[359–361] It may be more common than is generally appreciated, as it can resemble low-grade endometrioid carcinoma and many such tumors have undoubtedly been signed out as such in the past. The expression of TTF-1, CD10, and GATA3 and absence of ER and PR expression are helpful diagnostic features.

Histochemical and Immunohistochemical Features

Immunohistochemically, endometrial adenocarcinomas of the conventional (endometrioid) type are positive for keratin (especially keratins 7, 8, 18, and 19),[362,363] vimentin,[364,365] and PAX8.[366] Coexpression of keratin and vimentin is the norm.[367] Some tumor cells have also been found to contain glial fibrillary acidic protein.[363]

Estrogen and progesterone receptors are present in most cases of endometrial adenocarcinoma of endometrioid type, with low-grade tumors being almost invariably positive.[368–370] Expression of ER and PR is variable in high-grade endometrioid and serous carcinomas and uncommon in clear cell carcinoma.[371] A finding of diagnostic significance is that WT1, which is nearly always positive in serous tumor of the tube and ovary and its metastases, is generally negative or only weakly expressed in serous carcinoma of the endometrium,[372–374] as well as in other types of primary endometrial carcinoma.[375] A potential pitfall is represented by TTF-1, a marker classically associated with lung and thyroid carcinoma but which can be also be expressed in endometrial (and endocervical) adenocarcinoma.[376,377]

Note that there are no immunomarkers that are completely sensitive or specific for histotype, and the diagnosis of endometrial carcinoma histotype should be based on evaluation of H&E-stained slides. As mentioned previously, in the specific instance of a glandular neoplasm with "ambiguous features" (i.e. nuclear atypia that exceeds what is usually seen in low-grade endometrioid carcinoma but is insufficient to confidently diagnose serous carcinoma), p53 immunostaining can be used to help in the differential diagnosis between low-grade endometrioid and serous, with wild type p53 expression supporting the former diagnosis.[296]

Molecular Genetic Features

Earlier in this section we described how TCGA identified four subtypes of endometrial carcinoma, based on genomic features: type I/low somatic copy number abnormalities/p53 wild type (endometrioid, typically low grade); type II/high somatic copy number abnormalities/p53 abnormal (mostly serous with a few high-grade endometrioid); hypermutated/MMR deficient (mostly endometrioid); ultramutated/POLE exonuclease domain mutated (endometrioid, often high grade).[228–230,232] Up until now we have attempted to understand the molecular genetic features of endometrial carcinoma in the context of histotype, but in the future all molecular studies should take into account the four genomic subtypes.

The major genetic abnormalities that have been detected in endometrioid adenocarcinomas are mutations in the *PTEN* gene (most cases) and frequent mutations in *PIK3CA*, *KRAS*, *ARID1A*, and *CTNNB1*, whereas serous carcinomas have *TP53* mutations (>90% of cases).[382–389] Mutations in *PPP2R1A* are a feature of endometrial serous carcinomas but not serous carcinomas of tube and ovary.[390]

DNA aneuploidy is present in approximately one-fourth of endometrial carcinomas; positive tumors tend to be of advanced surgical stage and higher microscopic grade, associated with deeper myometrial invasion, and accompanied by lymph node metastases. As expected, aneuploidy is the rule in serous carcinoma but can also be seen in a minority of endometrioid carcinomas.[391,392]

Spread and Metastases

The two obvious sites of direct spread of endometrial carcinoma are the myometrium and the cervix, both of these having important prognostic connotations.[393] For staging purposes, myometrial invasion is divided into two stages: up to 50% of the myometrial thickness or invasion to 50% or more of the myometrial thickness. This apparently straightforward determination is actually fraught with many potential inaccuracies.[394] The arcuate vascular plexus of the myometrium has been used as a guideline for this measurement, in the sense that carcinomatous infiltration into or through this plexus can be taken as surrogate evidence that the tumor has invaded over 50% of the myometrium.[393] This can be a useful approach when the uterine corpus is distorted by leiomyomas, for example, making measurement of depth of invasion difficult. A particularly difficult situation arises if there is coexistent adenomyosis. On the one hand, involvement of adenomyosis foci by carcinoma can be overinterpreted as deep myometrial invasion; on the other, it has been claimed that involvement of adenomyosis by carcinoma is an indicator of the likely presence of true myometrial invasion elsewhere in the myometrium.[395]

Invasion of the endocervix by endometrial carcinoma is relatively common, and the histologic features were discussed previously.

Lymphovascular invasion is the most important route of spread of endometrial cancer. It has recently been shown that "substantial" rather than minimal or focal lymphovascular invasion is of prognostic significance; the prognosis of patients with one or two lymphatic channels containing tumors is indistinguishable from that of patients without lymphovascular invasion.[396] A warning here is in order. We are referring to the artifact known as *vascular pseudoinvasion* sometimes seen in laparoscopic hysterectomy specimens and characterized by conspicuous tumor fragments in the lumen of thick-walled vessels in the outer myometrium or in ectatic vessels anywhere in the myometrium. These tumor fragments are detached from the vascular wall, lack an inflammatory perivascular infiltrate, and are accompanied by tumor fragments in myometrial clefts.

The most common sites of extrauterine spread in endometrial adenocarcinoma of the endometrioid type are the pelvic and para-aortic lymph nodes and the ovaries (see next section). Nodal metastases occur in approximately 5%–25% of clinically stage I tumors and are more likely to occur in invasive high-grade tumors (even if such tumors are superficial), in large sized and/or deeply invasive tumors regardless of grade, in tumors with cervical extension, and in tumors with vascular invasion.[397–399]

Serous carcinoma has a particular propensity for lymph vessel permeation. Involvement of peritoneal surfaces (particularly in the pelvis) occurs early in the disease and can be present even at the intraepithelial stage.[400] In these cases, molecular analysis has shown that the disease is clonal, indicating origin at a single site with secondary early spread.[393,399,401] An additional route of spread of endometrial carcinoma is transtubal,[293,403] but another warning is in order. On occasion, the keratin present in endometrial carcinoma with squamous metaplasia desquamates into the uterine cavity and from there travels via the fallopian tube to produce implants on the peritoneal surface, leading to the formation of foreign body granulomas.[404] This finding should not be regarded as evidence of metastatic disease *in the absence of viable neoplastic cells*. Follow-up data on these patients suggest that these keratin granulomas have no prognostic significance.[405]

The most common sites of recurrence of endometrial carcinoma are the vaginal vault and pelvis. Serous carcinoma characteristically spreads throughout the abdominal cavity in a fashion similar to that of tubo-ovarian serous carcinoma. Metastases of endometrial carcinoma in the bladder can simulate a primary neoplasm of this organ.[406]

Distant metastases of endometrial carcinoma are more common in the lung, liver, bone, central nervous system, and skin. The latter tend to occur in the head and neck region, particularly the scalp.

Coexistent Uterine and Other Genital Tract Carcinomas

Approximately 8% of endometrial carcinomas are accompanied by a simultaneous **ovarian carcinoma.** When they are of similar microscopic types—which is usually the case—it has been difficult to decide whether there are two independent tumors or whether one of the sites represents a metastasis.[407] Features in the endometrial tumor that are considered to favor an independent primary are stage Ia, grade 1 or 2, without lymphovascular invasion, while the ovarian tumor should similarly be organ confined and low grade.[408] There is ample evidence, based on large case series, that these tumors behave as independent stage I primary tumors rather than as stage II ovarian carcinoma or stage III endometrial carcinoma.[407,409] High-grade tumors should be considered metastatic (almost always from endometrium to ovary, as discussed previously) until proven otherwise.[407] Other features considered to favor a metastatic nature for the synchronous ovarian tumor include the following: bilateral involvement, multinodular pattern of growth, presence of associated surface implants, and prominent lymphatic or vascular invasion within the ovarian stroma.[410] The clinical outcome data make interpretation of whole genome or whole exome sequencing data challenging, as these clearly indicate a clonal origin for synchronous ovarian and endometrial tumors in a large majority of cases.[411,412] The empirical evidence supports the practice of using the older clinicopathologic criteria in staging, as they result in the appropriately conservative treatment, and in this circumstance molecular testing results should not enter into the decision on whether to stage as independent primary tumors. Please note that in taking this pragmatic approach we are not suggesting that the synchronous tumors have risen independently; this would be akin to suggesting that, based on available evidence, the world is flat. We are simply advocating an approach to staging that is supported by clinical outcome data and will not lead to overtreatment of patients.

Endometrioid carcinomas have been described involving simultaneously the uterine corpus and the fallopian tube; in about half of them the fallopian tube tumors were located in the distal or fimbriated end, and some of the tumors were in situ.[413] Approximately 20% of serous carcinomas of endometrium are associated with metastatic tubal mucosal involvement.[293] We undoubtedly are seeing more cases of endometrial carcinoma with involvement of the fallopian tube mucosa since the introduction of more extensive sampling of tubal fimbria, but we do not yet know the clinical significance of this finding.

Treatment

The usual treatment of endometrial carcinoma is total abdominal hysterectomy with bilateral salpingo-oophorectomy. Whenever feasible, this should be supplemented by surgical staging (including biopsies of pelvic and para-aortic lymph nodes) if any of the following is present: greater than 50% myometrial invasion, grade III tumor, cervical involvement, extrauterine spread, unfavorable histologic component (serous, clear cell, or undifferentiated), or palpably enlarged nodes.[415] Radiation therapy, which was administered routinely in conjunction with surgery (either preoperatively or postoperatively), is no longer favored, except for patients with poor prognostic factors that put them at a high risk of recurrence.[416] This has largely been the result of randomized clinical trials showing that radiation therapy decreases local recurrences but does not influence disease specific or overall survival.[417]

Progestational agents can be curative for early stage, low-grade tumors, and in more advanced tumors, although usually not curative, occasionally induce striking temporary regressions in the primary tumor as well as in the metastases.[418,419] Well-differentiated carcinomas treated with progestins show a decreased gland-to-stroma ratio, decreased glandular cellularity, decreased or absent mitotic activity, loss of cytologic atypia, and a variety of cytoplasmic changes, including mucinous, secretory, squamous, and eosinophilic metaplasia.[420]

The treatment of serous carcinoma consists of hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and surgical staging, the latter including peritoneal cytology and pelvic and para-aortic lymph node sampling. This is usually followed by adjuvant therapy, except for the minimally invasive tumors.[421–425]

Tumor relapse may appear in the form of local recrudescence (50%), distant metastases (28%), or both (21%); the median interval is between 1 and 2 years.[426] Local recurrences can be treated successfully with aggressive radiation therapy.[427]

Prognosis

Factors of prognostic importance in endometrial adenocarcinoma are the following:

1. *Tumor stage*, as defined by the FIGO system.[428] As for most of the common epithelial malignancies, stage is the strongest prognostic indicator and all biomarkers must be evaluated for significance independent of stage.
2. Level of *infiltration* of the myometrial wall, as incorporated into the FIGO staging system.[461] Tumors with invasion of over onehalf of the myometrium fare worse than those invading less than one-half.[429–432] Among the latter (stage Ia tumors), there is no significant difference between those that invade up to one-third and those that invade greater than one-third but less than one-half.[433]
3. *Microscopic grade* of differentiation, as defined by the FIGO system.[431,434,435] As already stated, originally this system was primarily based on architectural rather than nuclear features, except for the serous and clear cell types, which are by definition high-grade tumors.[436] The addition of a nuclear parameter to the FIGO system has improved its prognostic significance.[437] High-grade tumors have a worse prognosis regardless of their histologic subtype.[438]
4. *Age.* Patient age has consistently been an important prognostic factor, with advanced patient age associated with worse outcomes, but this has recently been questioned; Haley et al., in a large series, showed no significance for age as a prognostic factor in patients with early stage endometrial carcinoma, when carefully matched for tumor grade/histotype and other pathologic variables.[439] This illustrates the difficulty in assessing the relative strength of prognostic markers, when they co-vary, as age does with type II/serous/advanced stage.
5. *Histotype*. Among high-grade tumors (grade III endometrioid, serous, and clear cell) some studies show that histotype is of prognostic significance while other studies do not; the likely explanation is that the grade III endometrioid carcinomas are a heterogeneous group, and include all four molecular subgroups (i.e. copy number low, copy number high, ultramutated and hypermutated), and the subgroups of grade III endometrioid as defined based on the genomic abnormalities have very different prognoses.[440]
6. *Lymph vessel invasion*. Tumor permeation of lymph vessels is a poor prognostic sign,[441,442] particularly if extensive.[396,444]
7. *Molecular subtypes:* The four molecular subtypes of endometrial cancer, identified based on TCGA study, were discussed previously in this section and have emerged as important prognostic subgroups of endometrial carcinoma (see Table 33.1).
8. *Others*. Parameters said to be indicative of favorable outcome are absence of L1CAM expression,[229] absence of β-catenin mutation,[229,446] and diploid cellular DNA content.[392,448]

Endometrial Stromal Tumors

Tumors composed of endometrial stroma tend to occur in middle-aged women (average age, 45 years) and often present with vaginal bleeding.[449]

Microscopically, the low-grade endometrial stromal neoplasms are composed of uniform, predominantly oval, small cells, very closely resembling those of the endometrial stroma, individually enveloped by reticulin fibers, which characteristically encircle small vessels that resemble spiral arterioles (Fig. 33.44).

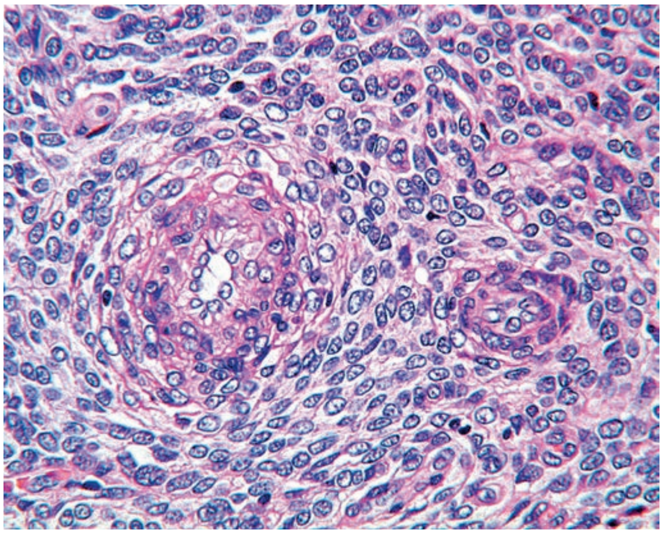


Figure 33.44 Typical microscopic appearance of low-grade endometrial stromal tumor, showing bland oval cells arranged concentrically around spiral arterioles.

Endometrial stromal tumors are divided into low-grade and high-grade stromal neoplasms; the former are further subdivided according to the type of margins into: (1) a benign category (endometrial stromal nodule) having pushing margins; and (2) a malignant category (low-grade endometrial stromal sarcoma) having infiltrating margins.[450–452] Distinction between endometrial stromal nodule and low-grade endometrial stromal sarcoma is made solely based on the margin between the tumor and myometrium, and it follows that this distinction is not possible based on endometrial biopsy/curettings. Endometrial stromal neoplasia is recognized in a biopsy/curetting by the presence of confluent areas of stroma measuring more than 5 mm, without glands; in such a case, one can only diagnose "low-grade stromal neoplasm" and defer definitive classification to the hysterectomy specimen.

Endometrial stromal nodules appear grossly as solitary sharply circumscribed masses of soft consistency and a characteristic yellow-to-orange color (Fig. 33.45). They do not invade veins, lymphatics, or the myometrium. The prognosis is excellent; recurrence did not occur in any of the 60 cases studied by Tavassoli and Norris,[430] even when some irregularities in the margin, high mitotic counts, or glandular foci were present. Cases in which the irregularities at the margins are pronounced but which lack the typical, usually extensive infiltration of the endometrial stromal sarcomas listed later have been referred to as *endometrial stromal tumors with limited infiltration*.[453] Their behavior seems to be as favorable as that of the conventional stromal nodules. Genetically, endometrial stromal nodule is characterized by t(7;17), which results in *JAZF1–JJAZ1* fusion.[454–456] The differential diagnosis is with cellular leiomyoma and markers of importance in this context are CD10 (consistently positive), h-caldesmon (consistently negative), and HDAC8 (consistently negative); note that desmin and smooth muscle actin may show weak immunoreactivity in low-grade endometrial stromal neoplasms.[457–461]

Low-grade endometrial stromal sarcomas infiltrate the myometrium and have a particular tendency to permeate lymph vessels (Figs. 33.46 and 33.47). The latter feature sometimes can be detected grossly by the presence of yellowish, ropy, or ball-like masses filling dilated channels. They may also present as polypoid masses (Fig. 33.48). The local invasion may extend into the broad ligament, tubes, and ovaries. Their low-power appearance is very distinctive, in the sense of showing extensive myometrial permeation by sharply defined tumor islands with pointed edges, somewhat reminiscent of those seen (in an altogether different context) in thymoma. Other commonly encountered features in low-grade endometrial stromal sarcomas include foci of hyalinization and scattered foamy cells.[462] Morphologic variations (other than those described in greater detail later) include the presence of a prominent fibrous or myxoid component,[463] adipose metaplasia,[464] a component of epithelioid cells with abundant eosinophilic cytoplasm,[465] scattered tumor cells

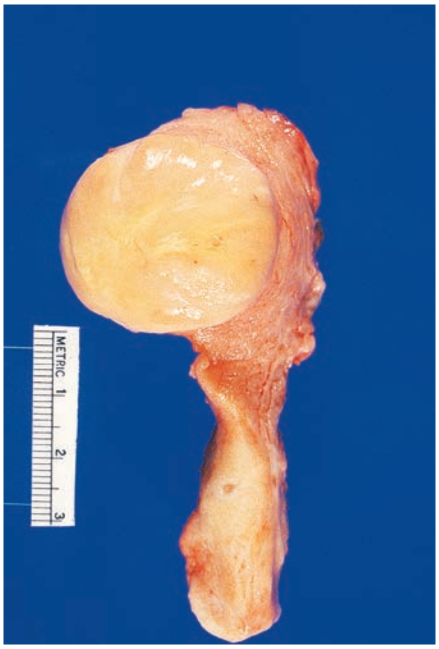


Figure 33.45 Endometrial Stromal Nodule. The lesion is characteristically well circumscribed and has a yellow color.

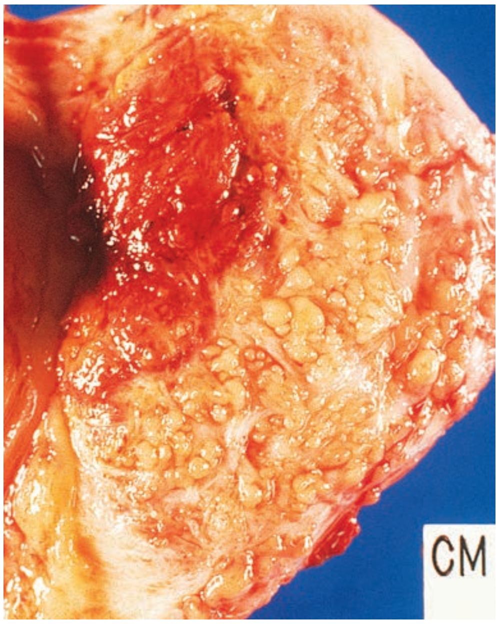


Figure 33.46 Low-grade endometrial stromal sarcoma showing diffuse permeation of the myometrium in the form of small nodules bulging on the cut surface.

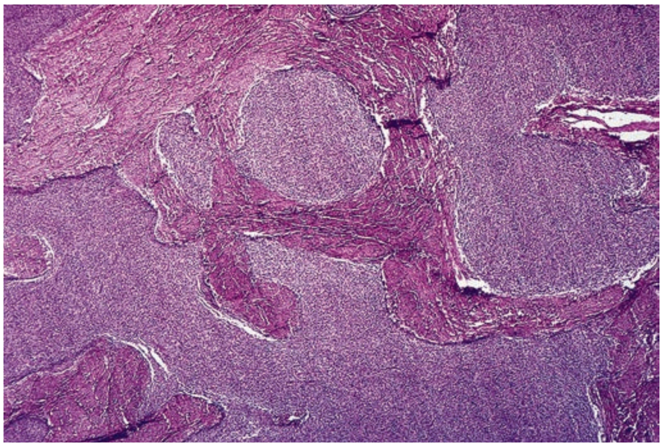


Figure 33.47 Typical low-power appearance of endometrial stromal sarcoma.

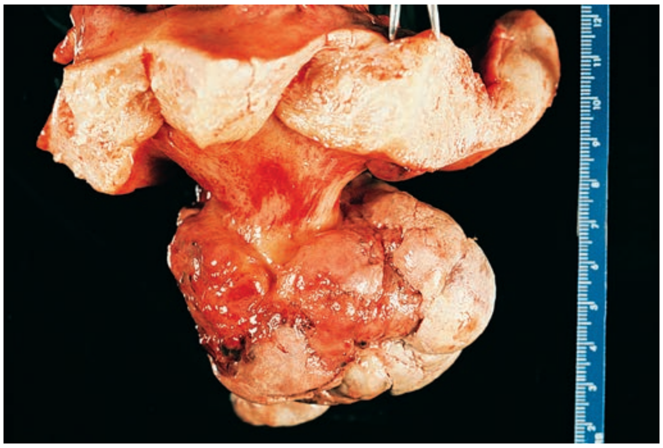


Figure 33.48 Low-grade endometrial stromal sarcoma presenting as a huge polypoid mass within the endometrial cavity. This pattern of growth is unusual in this tumor type.

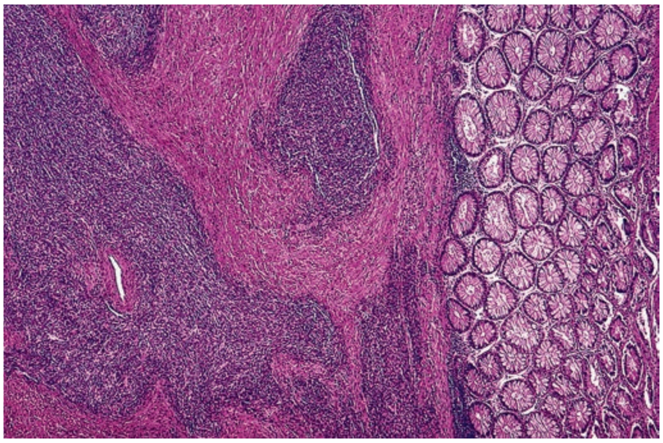


Figure 33.49 Low-grade endometrial stromal sarcoma metastatic to wall of large bowel.

with "symplastic" nuclei,[464,466] and papillary/pseudopapillary formations.[467]

The natural history of low-grade endometrial stromal sarcoma is characterized by slow clinical progression, repeated local recurrences (in the pelvis, ovary, intestinal wall, other intra-abdominal sites, and anterior abdominal wall), and occasional metastases (Figs. 33.49 and 33.50).[468]

Size of the tumor and extrauterine extension are important prognostic features. Low-grade stromal neoplasms less than 4 cm in diameter practically never recur, and tumors confined to the uterus at the time of the initial surgery infrequently do so.

The tumor cells contain estrogen and progesterone receptors, and the tumors respond to administration of progestins.[469,470] Genetically, about 50% of cases show t(7;17) with *JAZF1–SUZ12 (JJAZ1)* fusion (identical to that seen in endometrial stromal nodule, but differ in showing concurrent silencing of the unrearranged *SUZ12* allele). Other less common genetic abnormalities include t(6;7) with *JAZF1–PHF1* fusion, t(6 : 10) (*EPC1-PHF1*) and t(1 : 6) (*MEAF6-PHF1*).[454–456] These genetic findings may be utilized to aid in the diagnosis of endometrial stromal sarcoma by using fluorescence in situ hybridization (FISH) or reverse transcriptase-polymerase chain reaction (RT-PCR). It should be noted that as well as the translocations described previously, a significant minority of low-grade endometrial stromal sarcomas have rearrangement of JAZF1 or PHF1 by FISH, without identification of the fusion partner.[471]

The differential diagnosis between low-grade endometrial stromal neoplasm and a smooth muscle tumor was discussed previously, but a related issue is the phenomenon of tumors that show both endometrial stromal and smooth muscle differentiation, based on both light microscopic examination and immunostaining. If the smooth muscle differentiation is present in the form of an inconspicuous focus in the midst of an otherwise typical endometrial stromal tumor, it can be ignored for diagnostic purposes.[472] A distinct histologic pattern is the presence of relatively discrete nodules of small epithelioid tumor cells, which stain strongly with desmin, embedded in hyalinized collagen, the so-called "starburst" pattern.[473] If sizable (one-third or more of the tumor mass), the neoplasm is referred to as **combined smooth muscle–stromal tumor.**[474,473] These combined tumors often show the t(7;17) with *JAZF1–SUZ12* fusion characteristic of low-grade endometrial stromal neoplasms and behaviorally seem to be closer to endometrial stromal tumors than to smooth muscle tumors, and—on the whole—are very indolent; therefore, the diagnostic term *endometrial stromal sarcoma with smooth muscle differentiation* is commonly used.[474]

Epithelial-like formations may appear in endometrial stromal tumors in the form of solid masses, glandular structures, or anastomosing cords. Some of these formations have been likened to those of ovarian sex-cord neoplasms (particularly granulosa cell tumors) and the tumors containing them have been referred to as **uterine tumors resembling ovarian sex-cord tumors (UTROSCTs;** Fig. 33.51).[455,475] Some cases feature an epithelial retiform component resembling rete ovarii.[476] Their immunohistochemical and ultrastructural profile has varied considerably in the reported series, ranging from myogenous to epithelial.[477] However, at least some of the cases have shown a phenotype consistent indeed with a sex-cord line of differentiation, including reactivity for inhibin, CD99, and Melan-A.[478–481] Uterine tumors in which these structures predominate to almost the exclusion of others have generally behaved in a benign fashion,[475] but occasional metastasizing examples are on record.[482]

The uterine neoplasm known as **plexiform tumor** or **tumorlet** is an occasional incidental finding in a hysterectomy specimen. They are typically less than 1 cm and invariably benign. Their histogenesis is controversial, and they have been claimed to be of endometrial stromal,[483] myofibroblastic,[484] and smooth muscle derivation.[485,486]

A different type of epithelium-like formation that can be seen in endometrial stromal tumor is represented by **endometrioid**

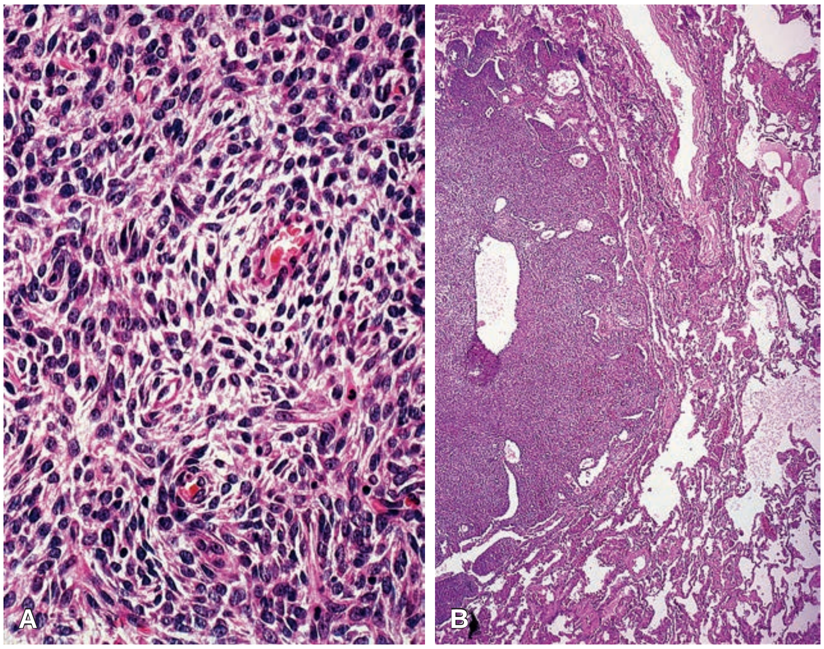


Figure 33.50 **A** and **B,** Low- and high-power appearance of low-grade endometrial stromal sarcoma metastatic to lung. This lesion may be misdiagnosed as spindle carcinoid tumor, hemangiopericytoma, or solitary fibrous tumor.

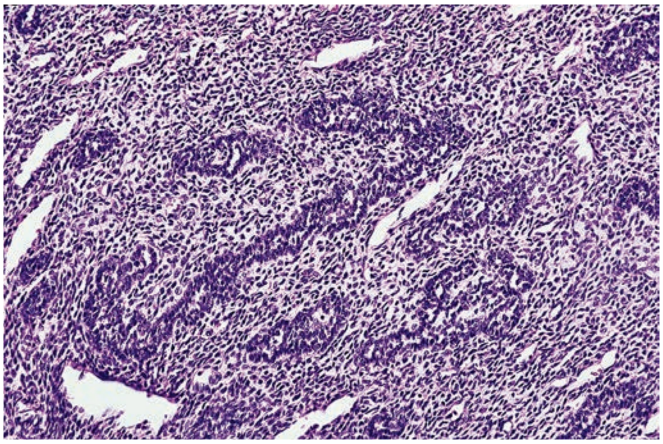


Figure 33.51 Low-grade endometrial stromal sarcoma with structures resembling ovarian sex cord tumors.

glandular foci having a benign, atypical, or carcinomatous appearance (Fig. 33.52).[487,488]

Tumors with the appearance of low-grade endometrial stromal neoplasms may be found in the cervix,[489] ovary, pelvis, and retroperitoneum.[490] Some of these are seen in association with endometriosis, from which presumably they have arisen.[491] These extrauterine tumors may have any of the morphologic features and variations described in connection with the uterine neoplasms, including ovarian sex cord–like structures and endometrioid glandular proliferation.[492] A note of caution is in order. Before making a diagnosis of primary extrauterine low-grade endometrial stromal tumor, one should make an effort to rule out a metastasis from a uterine lesion, knowing that these metastases are often solitary and that they can occur years or decades after the excision of the original tumor, which (to complicate things further) might have been misdiagnosed as a peculiar-looking smooth muscle tumor.[493,494]

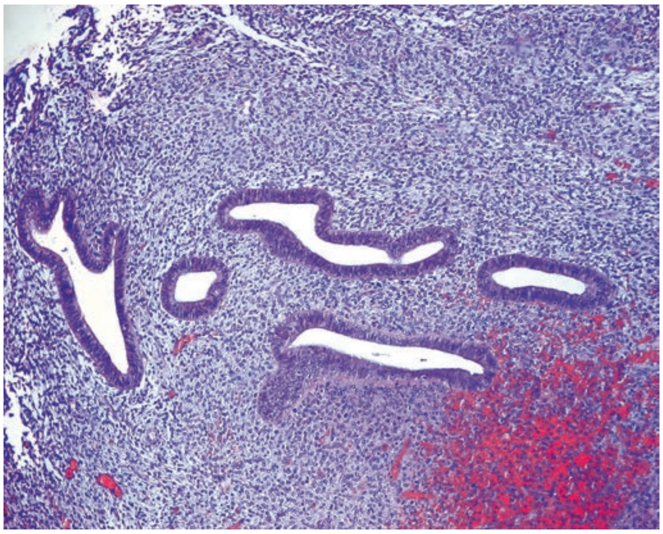


Figure 33.52 Peritoneal metastasis from endometrial stromal sarcoma accompanied by benign endometrioid glands.

High-grade endometrial stromal sarcoma is a rare tumor; however, as it was only recently described, the true incidence is unknown. On low power it infiltrates the myometrium in a manner similar to that of low-grade endometrial stromal sarcoma.[495] The microscopic appearance is variable, ranging from low-grade spindle cell areas to a high-grade uniform small round cell component (Fig. 33.53).[496] It lacks conspicuous pleomorphism, which sets it apart from undifferentiated uterine sarcoma (see later). The mitotic activity is typically greater than 10 MF/10 HPF, in contrast to low-grade endometrial stromal sarcoma. The high-grade component of these tumors is negative for ER, PR, and CD10 but positive for expression of cyclin D1 (which unfortunately is not a specific marker of this tumor) and also express c-kit/CD117.[497] The low-grade

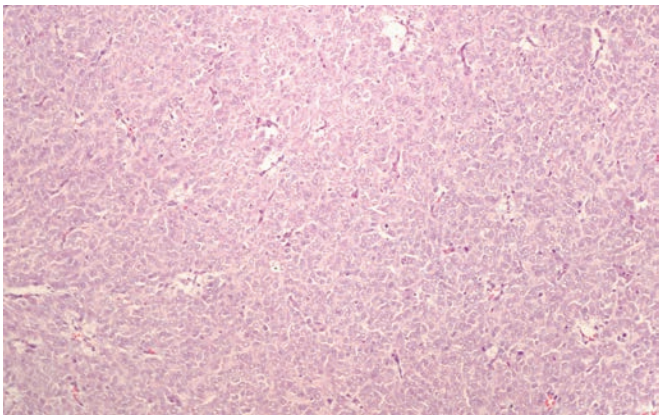


Figure 33.53 High-grade endometrial stromal sarcoma with t(10 : 17) *YWHAE-NUTM2* translocation. The nuclei are higher grade than in low-grade endometrial stromal sarcoma. (Courtesy Dr. Lien Hoang, Vancouver.)

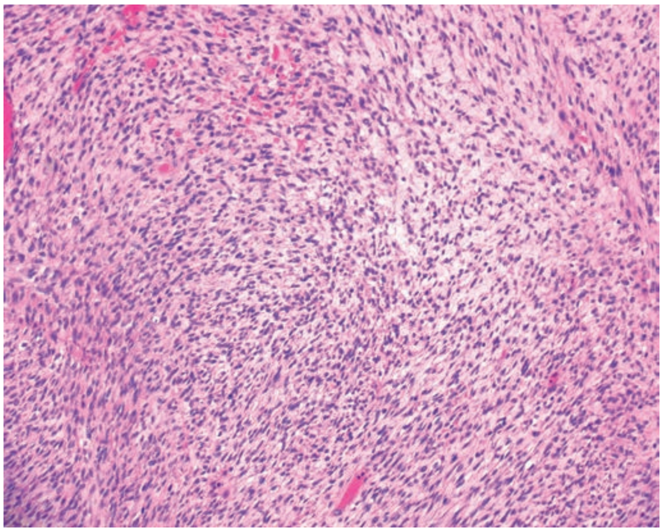


Figure 33.54 Myxoid high-grade endometrial stromal sarcoma with *Z3H7B-BCOR* translocation. (Courtesy Dr. Lien Hoang, Vancouver.)

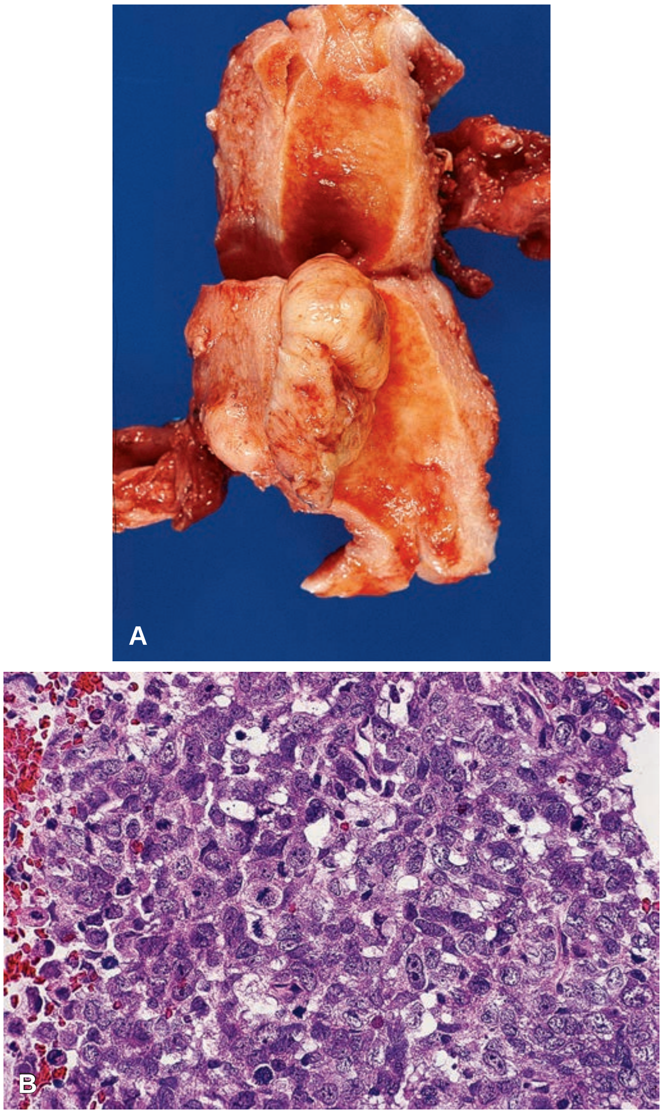


Figure 33.55 **A** and **B,** Gross and microscopic appearance of undifferentiated uterine sarcoma.

spindle cell component shows a more conventional endometrial stromal cell immunophenotype (ER, PR and CD10 positive). These tumors are characterized by t(10 : 17) with fusion of *YWHAE* and *NUTM2* (formerly known as *FAM22*). Genetic testing, for example, FISH, is an important diagnostic adjunct.[498] The prognosis of high-grade endometrial stromal sarcoma is intermediate between that of low-grade endometrial stromal sarcoma and undifferentiated uterine sarcoma. Responses to anthracycline chemotherapy have been reported and accurate diagnosis is important in guiding management.[499]

A second variant of high-grade endometrial stromal sarcoma has been described, characterized by spindled cells with abundant myxoid stroma and brisk mitotic activity, an appearance mimicking that of myxoid leiomyosarcoma (Fig. 33.54).[500] These tumors have *ZC3H7B-BCOR* gene fusion and follow an aggressive clinical course.

Recent studies suggest that BCOR immunohistochemical staining may serve as a sensitive and specific surrogate for identifying high-grade endometrial stromal sarcomas, regardless of the underlying genetic alteration (i.e. tumors with *BCOR* and *YWHAE* alterations are both immunoreactive).[501]

Undifferentiated uterine sarcoma shows a marked degree of nuclear pleomorphism and atypicality and lacks the vascular pattern and other distinctive features of endometrial stromal sarcoma (Fig. 33.55). It is an altogether different neoplasm from the lower grade, translocation-driven sarcomas described previously and behaves in a very aggressive manner. It is may prove to be a mixed group, histogenetically, with some being of endometrial stromal cell or smooth muscle cell origin, and others being monophasic carcinosarcoma, which it resembles morphologically.

Müllerian Adenosarcoma and Related Tumors

Müllerian adenosarcoma is a distinctive type of uterine tumor, consisting of sarcomatous stroma, typically low grade, and benign glandular elements.[502–504] It usually presents in elderly individuals as a bulky polypoid growth filling the endometrial cavity, less commonly as an intramural nodule (Fig. 33.56). Microscopically, it can bear a striking similarity to phyllodes tumor of the breast (Fig. 33.57). The stromal elements usually resemble endometrial stroma by light and electron microscopic examination but are more

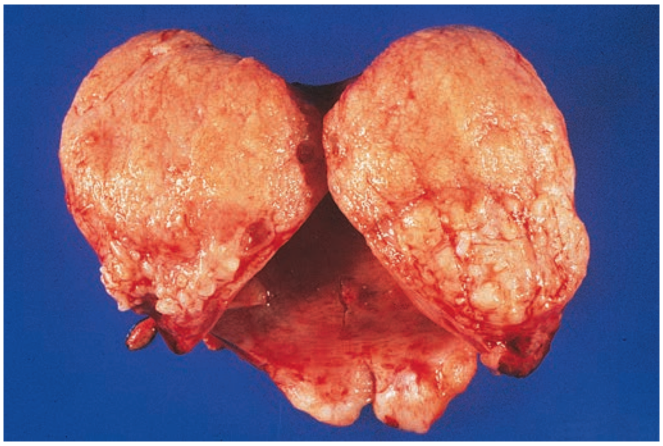


Figure 33.56 **Müllerian Adenosarcoma.** The tumor shows less degree of necrosis and hemorrhage than the usual malignant mixed müllerian tumor.

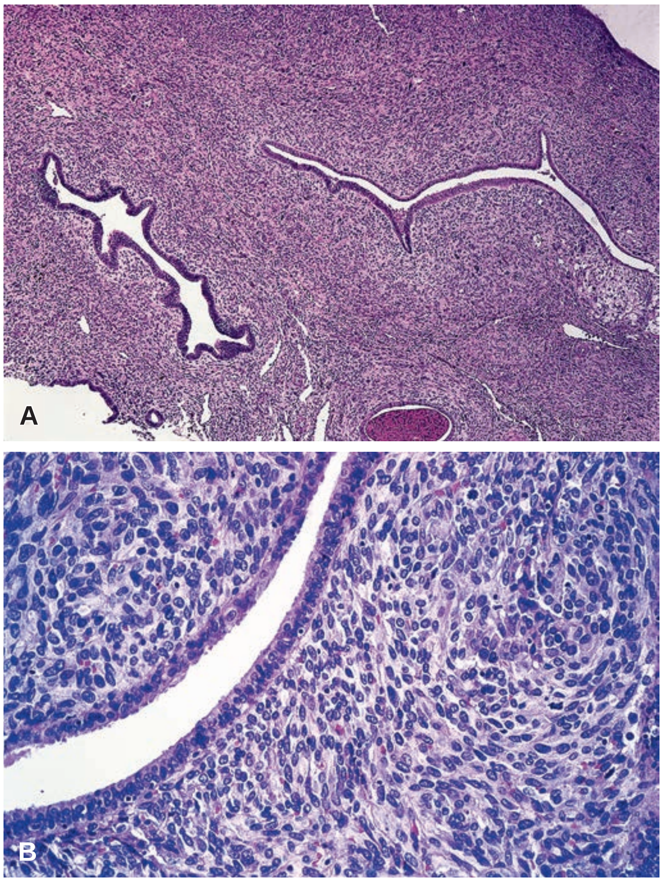


Figure 33.57 **A** and **B,** Low- and high-power view of müllerian adenosarcoma. The resemblance to phyllodes tumor of breast is obvious.

spindled.[505,506] As a rule, they do not appear as bizarre and undifferentiated as in the classic MMMT, although multinucleated giant cells and heterologous elements occur in approximately 20% of cases. The latter are usually of skeletal muscle type, but peculiar components such as angiosarcoma have also been observed.[507,508] Extensive areas of stromal fibrosis may result in a deceptively benign appearance.[503]

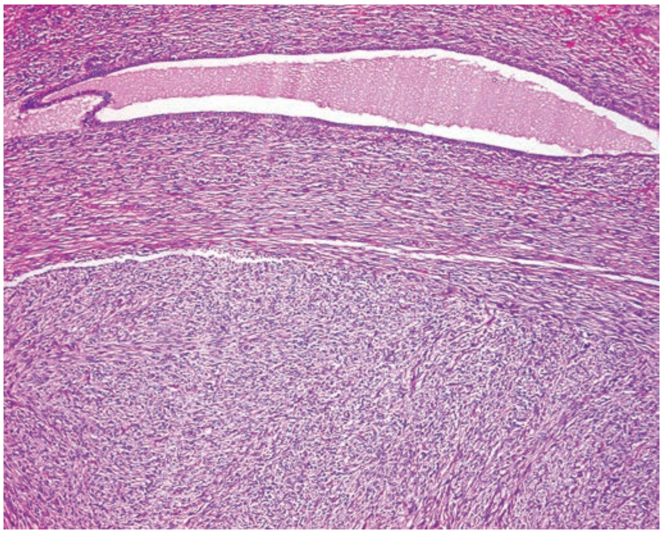


Figure 33.58 Müllerian adenosarcoma *(top)* with sarcomatous overgrowth *(bottom)*.

Like phyllodes tumor of the breast, müllerian adenosarcomas can show overgrowth by a pure sarcoma having a higher grade and exhibiting a greater mitotic rate than the sarcomatous component of the associated adenosarcoma (Fig. 33.58). These *müllerian adenosarcomas with sarcomatous overgrowth* behave in an aggressive fashion and are often associated with postoperative recurrence or metastases and a fatal outcome, in contrast to the usually indolent behavior of usual adenosarcoma.[504,509] The presence of high-grade cytologic features and sarcomatous overgrowth occur together and the prognostic significance of just high-grade cytologic features OR sarcomatous overgrowth in a low-grade tumor is not clear, as very few cases have been reported.

In the past, **uterine adenofibroma** was recognized as a benign counterpart of adenosarcoma.[510–513] The dividing line between the two groups was never sharp,[514] and it is clear that tumors with the characteristic features of uterine "adenofibroma" have occasionally been found to invade myometrium and pelvic veins, so it is now recommended that all such tumors be diagnosed as adenosarcoma.[515] Cases have been reported of adenosarcoma involved by adenocarcinoma.[516]

Leiomyoma

Leiomyomas of the uterus are extremely common neoplasms. The overall incidence is between 4% and 11%, but it rises to nearly 40% in women over the age of 50 years. Clinically apparent lesions are less common in parous than nulliparous women and premenopausal than postmenopausal women.[517] They are known to shrink after menopause; this is associated both with fibrosis and with a reduction in the size of the individual tumor cells.[518,519] The normal myometrium of leiomyoma-containing uteri expresses higher levels of estrogen receptors, a fact that may be related to their pathogenesis.[520] Leiomyomas are much more common in black women, in whom they have a tendency to be very numerous (Fig. 33.59).

Many of these tumors are small and go undetected; a systematic and meticulous study of 100 consecutive hysterectomy specimens revealed leiomyomas in 77 of them, 84% of the tumors being multicentric.[521]

These tumors occur subserosally, intramurally, or submucosally (Fig. 33.60) and produce symptoms referable to their size and location. The conventional teaching (which, like most conventional

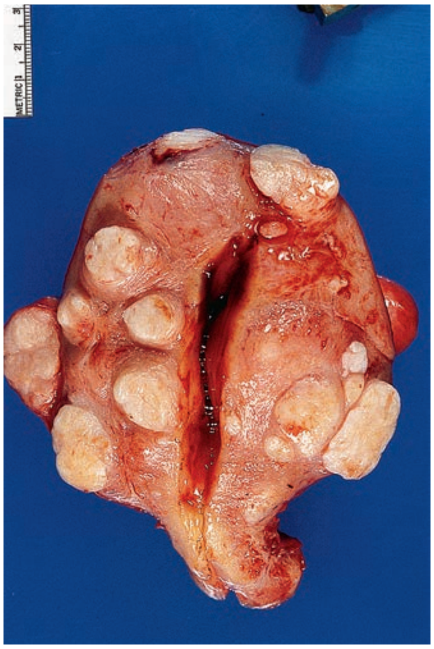


Figure 33.59 Multiple uterine leiomyomas.

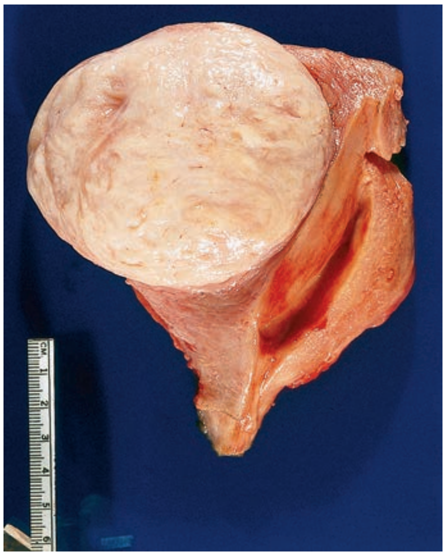


Figure 33.60 Large uterine leiomyoma with intramural and subserous involvement.

teachings, is only partially true) is that the submucous tumors produce metrorrhagia, sometimes massive, (because of endometrial ulceration), the intramural ones result in menorrhagia (because they interfere with myometrial contraction), and the subserosal ones usually remain asymptomatic. They may become large enough to block the ureters, interfere with pregnancy, or cause inflammatory complications. In rare instances, uterine leiomyomas have been associated with polycythemia, which regressed after the tumor was excised ("myomatous erythrocytosis syndrome").[522] These tumors, which are usually very large, have been shown to be the source of erythropoietin.[523]

Submucosal tumors often result in secondary endometrial changes that range from gland distortion to atrophy and ulceration. They may fill the endometrial cavity and emerge from the cervical canal as polypoid growths ("myoma nascens"). Under these circumstances, their surface is usually ulcerated and infected, the gross appearance thus simulating that of a malignant neoplasm.

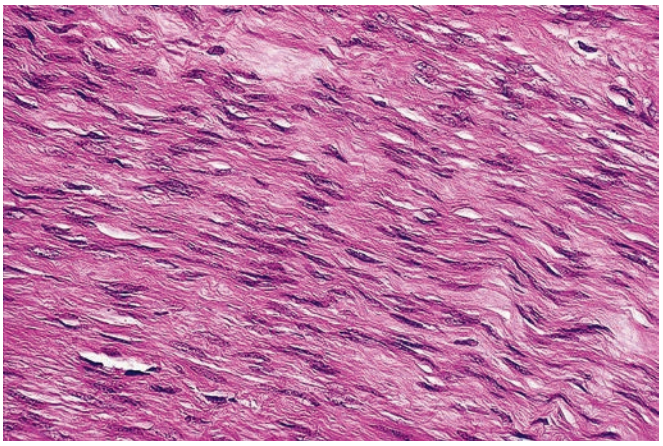


Figure 33.61 Elongated spindle cells with fibrillary acidophilic cytoplasm in the usual type of uterine leiomyoma.

It may be difficult to make a diagnosis of leiomyoma when only a few small fragments of smooth muscle are present in a curettage specimen. Unless these fragments show an obvious increase in cellularity or decreased cellularity/hyaline changes, one is unable to decide whether they originated in a submucosal leiomyoma or whether they represent normal superficial myometrium.

Grossly, the cut surface of a typical leiomyoma has a white whorled appearance that has been likened to raw silk. Microscopically, the tumor is formed by interlacing bundles of smooth muscle cells separated by a greater or lesser amount of well-vascularized connective tissue (Fig. 33.61). Ultrastructurally, the features are those of smooth muscle cells with varying degrees of differentiation.[524] Exceptionally, the tumors may contain skeletal muscle–like cells (which, however, lack cross striations and are myogenin negative; see also under Leiomyoma variants) and rhabdoid cells.[525] The stroma may contain a scattering of lymphocytes. Mast cells are often conspicuous, in contrast with leiomyomas of other sites.[526,527] On average, they are more numerous in cellular leiomyomas and leiomyomas with bizarre nuclei than in either ordinary leiomyomas or leiomyosarcomas.[522]

Cytogenetic alterations are common in uterine leiomyomas. The most consistent are rearrangements of 6p (involving the *HMGA1* gene), del(7q), +12 (involving the *HMGA2* gene), and t(12;14) (involving the *HMGA2* gene).[528-532] These have led to the discovery that disruptions or dysregulations of the high-mobility group proteins HMGA1 and HMGA2 contribute to the development of these tumors.[410,533] Mutations in *MED12* are present in most conventional leiomyomas but are less common in some leiomyoma variants.[534,535]

The treatment of uterine leiomyomas (including that of most of the many variants listed later) varies depending on the size and number of lesions, the age of the patient, and her desire to have children. Most asymptomatic leiomyomas need not be excised. Symptomatic neoplasms can be treated by hysterectomy or, in the case of patients who desire to become pregnant, by myomectomy.[536] Medical therapy includes administration of gonadotropin-releasing hormone analogs, such as leuprolide acetate depot. This may result in a decrease in the size of the leiomyoma—probably as a result of ischemic injury and cellular atrophy—but it does not result in significant pleomorphism or increased mitotic activity.[537–541] The decrease in cell size and increase in collagenization have also been documented at the ultrastructural level.[542] Other authors have reported tumor infiltration by lymphocytes of predominantly T-cell type[543,544]

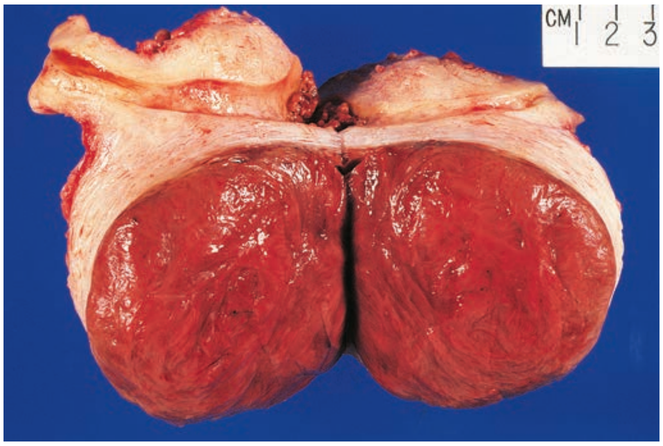


Figure 33.62 This uterine leiomyoma has undergone massive so-called red degeneration.

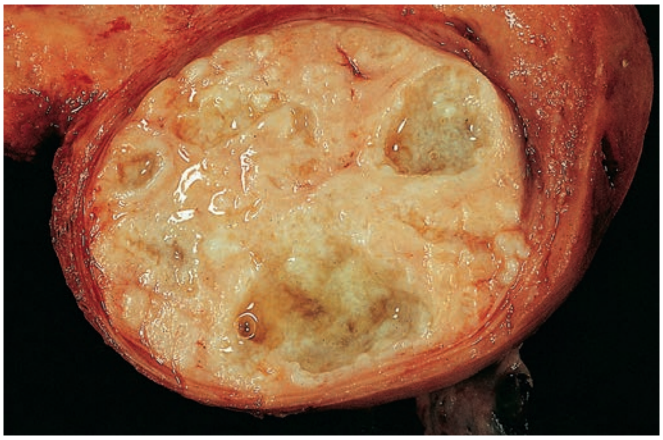


Figure 33.63 Leiomyoma with edematous (hydropic) changes leading to the formation of cystic cavities. (Courtesy Dr. Pedro J. Grases Galofré; from Grases Galofré PJ. *Patología ginecológica. Bases para el diagnóstico morfológico*. Barcelona: Masson; 2002.)

and vasculitis.[545] Immunohistochemically, leuprolide-treated leiomyomas show a decrease in cell proliferation indices and in hormone receptor expression.[546] Selective progesterone receptor modulators are increasingly used to treat symptomatic leiomyomas, as they have been shown to be effective for both a single course of therapy and repeated treatments.[547] Pathologists should be aware of the effects of these agents on the endometrium, described earlier in this section.

Another treatment modality for uterine leiomyoma is arterial embolization with tris-acryl gelatin microspheres.[548] This results in massive necrosis, sometimes accompanied by calcification, thrombosis, and a foreign body-type reaction to the injected material.[549,550] Infarct-type necrosis has also been observed in uterine leiomyomas of women treated with tranexamic acid, an antifibrinolytic agent.[551]

Leiomyoma Variants

Many variations on the basic theme previously described exist. Most of these are the result of secondary changes and are detectable in approximately 65% of cases. These include hyaline degeneration (63%), myxoid changes (19%), calcification (8%), cystic changes (4%), and fatty metamorphosis (3%). There is no relation between symptomatology and the presence of these changes.[552]

Red degeneration (present in 3% of cases) can result in abdominal pain, vomiting, and fever. This change is characterized grossly by a bulging surface and a homogeneous dark red appearance and microscopically by extensive coagulative necrosis. It may be associated with pregnancy or the use of contraceptive drugs (Fig. 33.62).

Apoplectic leiomyoma is pathogenetically related to red degeneration and is characterized by stellate zones of recent hemorrhage within nodules of hypercellular smooth muscle, with few or no mitotic figures.[553] Many variations on this basic theme exist, some of which can simulate malignancy.[554]

Hydropic degeneration is characterized by the accumulation of edema fluid, often associated with collagen deposition. It may have a diffuse, perinodular, or other patterns (Figs. 33.63 and 33.64).[555,556] The appearance may simulate intravenous leiomyomatosis or myxoid leiomyosarcoma.[555] Regarding the latter, leiomyomas with hydropic degeneration have a delicate filigree pattern rather than thick fascicles, and the extracellular material is edema fluid rather than mucopolysaccharides. Also, the presence of medium- to large-caliber blood vessels "floating" in the extracellular material is more characteristic of hydropic change.

Myxoid leiomyoma must be distinguished from both hydropic degeneration and myxoid leiomyosarcoma. The latter is recognized because of the presence of destructive myometrial invasion and the conventional features of malignancy.[557]

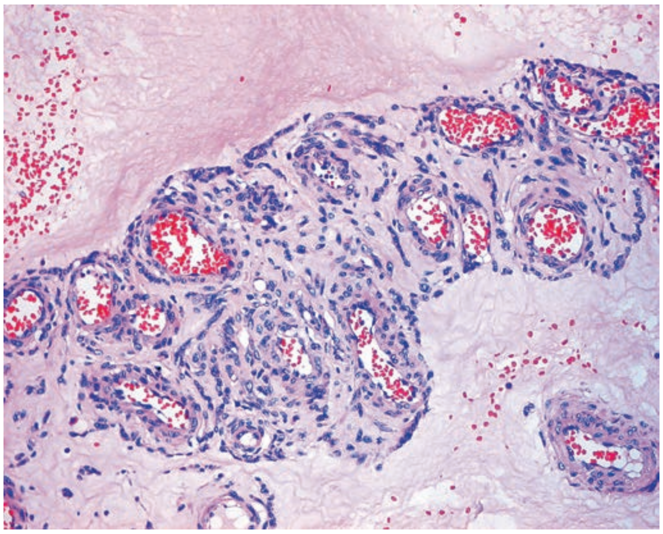


Figure 33.64 So-called perinodular hydropic degeneration in uterine leiomyoma.

Leiomyoma with lymphoid infiltration may simulate a malignant lymphoma because of the massiveness of the inflammatory component, which is made up of small lymphocytes, immunoblasts, and plasma cells.[558] Germinal centers may be present. The surrounding myometrium is relatively unaffected.[559,560] A variation on the theme is represented by the leiomyomas with a heavy infiltration by eosinophils.[561]

Cellular leiomyoma is a term reserved for those tumors having markedly increased cellularity but no coagulative necrosis, atypia, or an excessive number of mitotic figures (Fig. 33.65). It is a diagnosis that should be used sparingly; many leiomyomas can be more cellular than the surrounding myometrium, but the designation of cellular leiomyoma should be made only for tumors at the upper end of this spectrum of increased cellularity. Their natural history is the same as for the ordinary leiomyoma. The differential diagnosis includes leiomyosarcoma and endometrial stromal neoplasms.[562] At the cytogenetic level, cellular leiomyoma has been

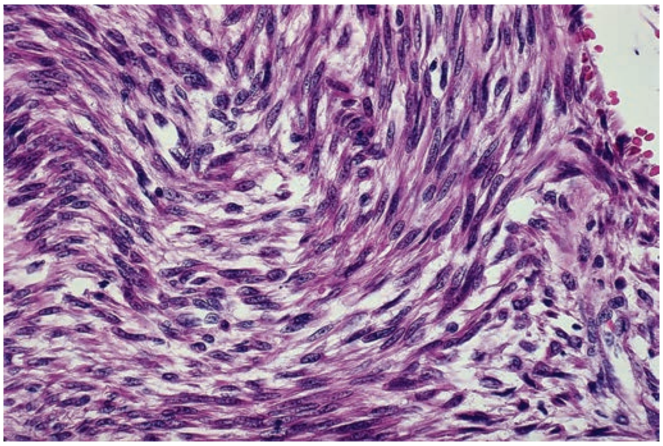


Figure 33.65 **Cellular leiomyoma.** There is no pleomorphism, undue mitotic activity, or necrosis.

found to be accompanied by loss of almost the entire short arm of chromosome 1.[563]

Leiomyoma with bizarre nuclei (also referred to in the past as atypical, bizarre, symplastic, or pleomorphic leiomyoma) contains foci with bizarre tumor cells showing variation in size and shape, hyperchromatic nuclei, and multinucleated forms but no infiltration of myometrium, coagulative necrosis, or increased mitotic activity (Fig. 33.66).[564] Rarely, the entire tumor is composed of such cells. The usual assumption has been that the symplastic cells represent a degenerative phenomenon, but they have been shown to be actively proliferating.[565] There should be no more than an occasional mitotic figure or the designation of smooth muscle tumor of uncertain malignant potential (STUMP) should be used (see later).

Mitotically active leiomyoma refers to tumors having from 5 to 15 mitotic figures per 10 HPF but lacking coagulative necrosis or cytologic atypia (Fig. 33.67).[566,567]

Leiomyolipoma (lipoleiomyoma) contains an admixture of smooth muscle and mature adipose tissue (Fig. 33.68).[568-571] It is believed that some of these tumors and the even rarer **lipomas** result from adipose metaplasia in leiomyomas.[569,572] The differential diagnosis includes lipid-rich angiomyolipomas (PEComas), which are HMB-45 positive (see later).[573] **Palisaded leiomyoma** is characterized by a degree of nuclear palisading such as to simulate a schwannoma.[574]

Epithelioid leiomyoma is partially or totally composed of rounded or polygonal cells (Fig. 33.69). Mixtures of epithelioid, clear cell, and plexiform patterns occur frequently enough to suggest that they represent variants of a single entity.[575,576] A transition to typical smooth muscle is sometimes observed. Morphologically similar tumors occur in the round ligament.[577]

Cotyledonoid dissecting leiomyoma is so designated because its gross appearance resembles that of placental tissue. The tumor is exophytic, bulky, and extends from the uterine wall into the broad ligament and pelvic cavity.[578,579] Microscopically, the appearance is that of a leiomyoma with extensive degenerative changes (Fig. 33.70). Despite its dissecting pattern, it lacks vascular invasion and is benign. Variations exist of leiomyomas that are cotyledonoid but not dissecting,[580] and dissecting but not cotyledonoid.[581,582] Believe it or not, there is also a cotyledonoid hydropic intravenous leiomyomatosis.[583]

Parasitic leiomyoma is the term given to the uterine leiomyoma that has become separate from the uterus and has acquired vascular connections with the omentum, pelvic wall, or other intra-abdominal sites, such as the cecal wall. The low-lying retroperitoneal smooth

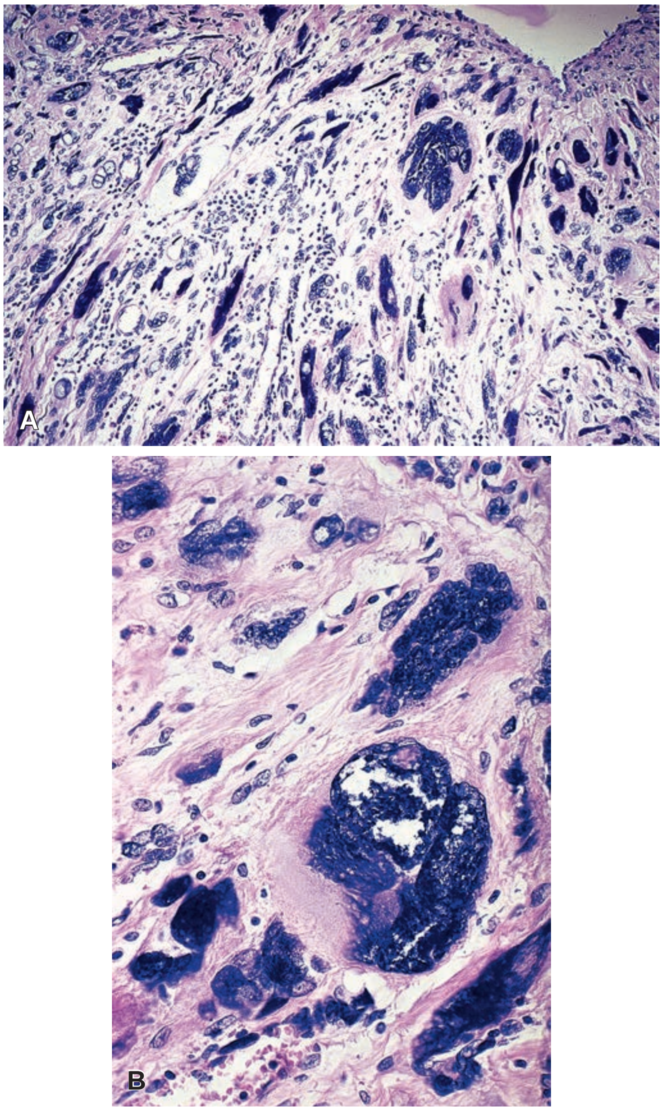


Figure 33.66 **A** and **B,** Two views of leiomyoma with bizarre nuclei. The size of some of the tumor cell nuclei makes them almost visible to the naked eye.

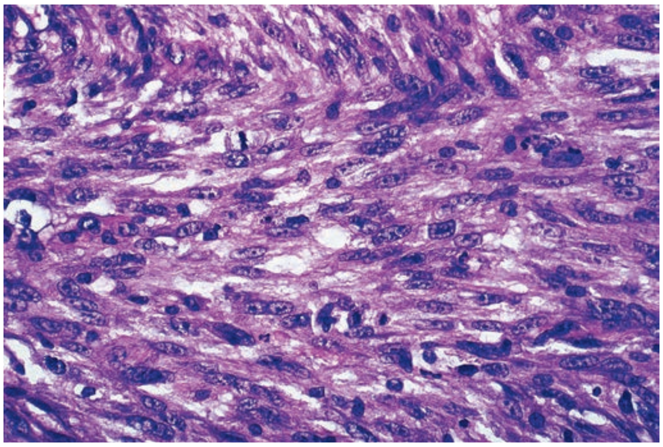


Figure 33.67 **Mitotically Active Leiomyoma.** There is also hypercellularity but no pleomorphism or necrosis.

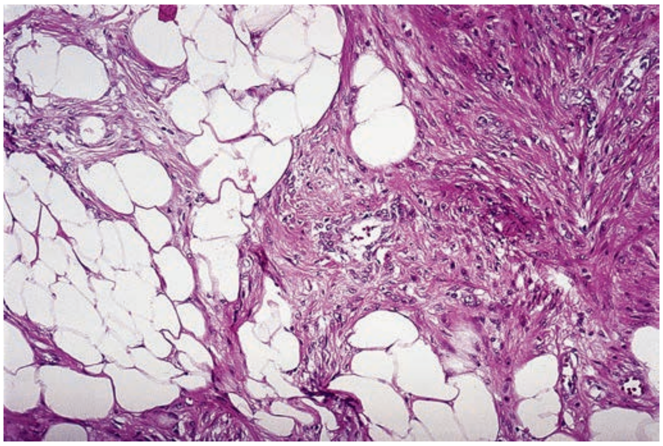


Figure 33.68 Admixture of mature smooth muscle and adipose tissue in leiomyolipoma.

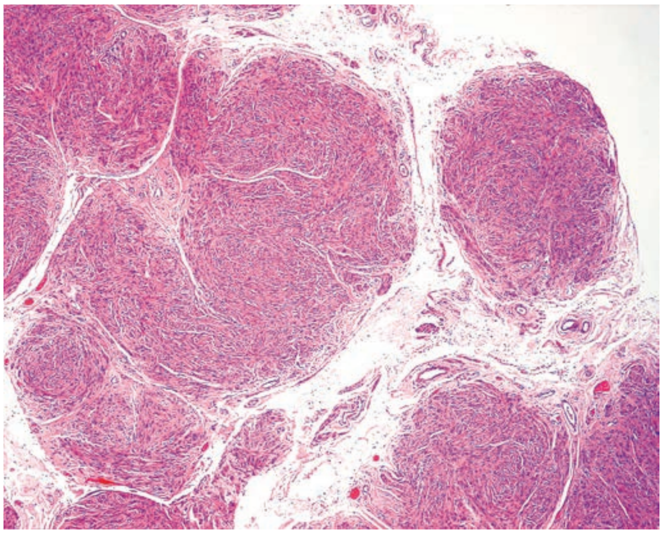


Figure 33.70 Micronodular microscopic appearance of uterine leiomyoma having the gross appearance of so-called cotyledonoid dissecting type.

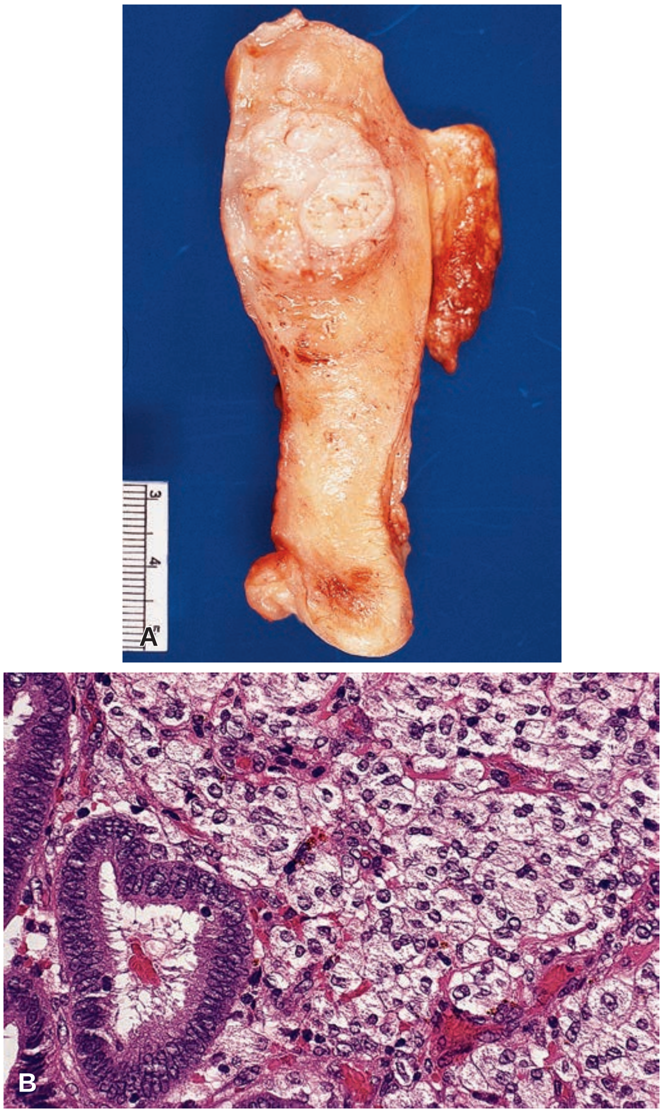


Figure 33.69 Epithelioid Leiomyoma. A, Gross appearance; **B,** microscopic appearance. The tumor cells have a round shape and an artifactually clear cytoplasm.

muscle tumors occurring in females and behaving in a benign fashion probably belong to this category, in the sense of being composed of myometrium-type smooth muscle, whether they actually arise from the myometrial wall or not.[584] Expression of estrogen receptor is a feature of smooth muscle tumors of the female reproductive tract; ER is rarely expressed in non-gynecologic smooth muscle tumors.[585]

Leiomyoma with skeletal muscle differentiation has been reported as an exceptional event.[586,587]

Angioleiomyoma (vascular leiomyoma) is a variant of uterine leiomyoma characterized by a swirling of the spindle cells around myometrial vessels, similar to that seen in the homonymous tumor of soft tissues. This tumor is thought to arise not from the parenchymal myometrial cells (as all other uterine leiomyomas are presumed to), but rather from the smooth muscle cells of the vessel walls.[588]

Diffuse leiomyomatosis is the term given to involvement of almost the entire myometrium by innumerable, ill-defined leiomyomas, many of microscopic size.[589,590] Clonality analysis done in a case of this condition supports the interpretation that these minute leiomyomas are independent tumors.[591] This extremely rare condition, which is probably analogous to so-called *seedling leiomyomas*,[592] should be distinguished from the nebulous *primary myometrial hypertrophy* or *myometrial hyperplasia*, defined as a uterus weighing over 120 g in the absence of any mass-like myometrial lesion.[593,594]

Hereditary leiomyomatosis and renal cancer syndrome is a rare autosomal dominant condition in which there is a germline mutation in the fumarate hydratase gene. Patients with this syndrome typically have multiple leiomyomas at an early age and the tumors are characterized by atypical nuclei with prominent nucleoli and occasional multinucleate forms.[595,596] While other histologic features have been described in the uterine tumors, such as perinucleolar halos (as also seen in the kidney tumors), hemangiopericytomatous vasculature, and brightly eosinophilic globules,[596,597] it is not possible to reliably recognize the syndromic leiomyomas based on H&E; immunostaining for overexpression of S-(2-succinyl) cysteine (2-SC) can serve to identify those tumors associated with the syndrome.[598]

Intravenous leiomyomatosis is an extremely rare condition characterized by the growth of mature smooth muscle inside the

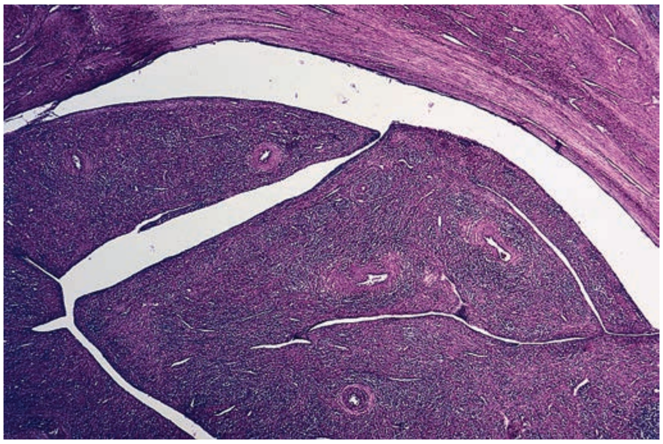


Figure 33.71 Large plugs of mature smooth muscle filling the vascular lumina in intravenous leiomyomatosis.

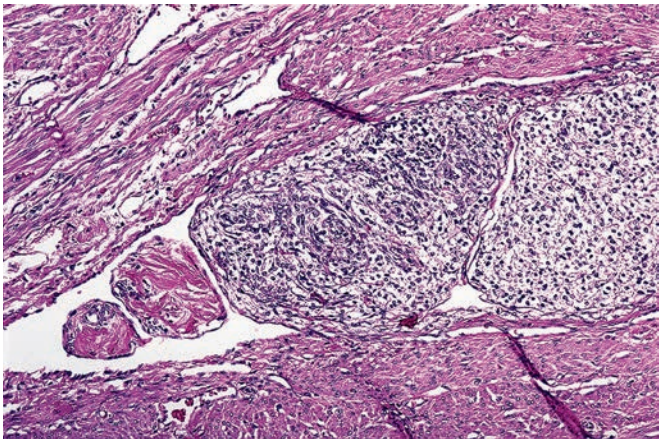


Figure 33.72 Intravenous leiomyomatosis composed of clear smooth muscle cells.

lumen of uterine and pelvic veins (Figs. 33.71 and 33.72).[599,600] It is often associated with typical uterine leiomyomas.[601] The clinical and gross features are similar to those of low-grade endometrial stromal sarcoma, but grossly apparent involvement of veins is more prominent. At the microscopic level, intravenous leiomyomatosis is composed of elongated smooth muscle cells, whereas endometrial stromal sarcoma is made up of round or oval endometrial stromal cells. Mitotic figures are rare or absent. The vessel permeation often extends to vessels in the broad ligament and in uterine and iliac veins; from there, it can proceed along the vena cava and even reach the right atrium.[602] However, distant metastases are exceptionally rare, and the long-term prognosis is excellent.[603] Cases have been described in which the microscopic appearance of the intravenous masses was that of lipoleiomyomas,[604] and others in which the intravenous leiomyomatosis was associated with a benign metastasizing leiomyoma in the lung.[605]

Benign metastasizing leiomyoma is the name given to the uterine tumor having the typical features of a leiomyoma (sometimes on the cellular side but invariably lacking coagulative necrosis, increased mitotic activity, and significant atypia) which is accompanied by nodules in the lung, regional lymph nodes, or other sites having a similar appearance and presumably representing metastases from it.[606] The extrauterine nodules may be just as bland-looking as the original uterine tumor or show features of leiomyosarcoma or STUMP.[607] The interval between hysterectomy and the appearance of the lung nodules is, on average, 15 years. The nodules tend to be multiple, and they have an average size of approximately 2 cm. The patients tend to be younger than those with conventional leiomyosarcoma, and the clinical course is much more indolent, with a median survival of 94 months after the excision of the metastases.[608] Some of these occurrences may be explained on the basis of inadequate sampling of the original tumor, but the fact that in many instances the extrauterine foci have a microscopic appearance that is just as bland suggests that this cannot be the explanation for the entire category. Parenthetically, the similarities with ordinary leiomyomas also apply to their hormone receptor profile (high) and proliferative activity (low).[608,609] They also can show deletion of the long arm of chromosomes 19 and 22.[610] Another possibility that has been advanced is that the extrauterine foci represent independent neoplasms.[611] However, the fact that they have been found to be clonally related speaks in favor of metastasis from a uterine neoplasm.[612,613]

Although this occurrence is unsettling, it is entirely credible. Other examples of tumors that generally behave in a benign fashion but once in a great while result in metastases having the same "benign" appearance certainly exist, benign mixed tumor of the salivary gland being a prime example. We simply have to accept the fact that tumors do not need to have the conventional morphologic attributes of malignancy to be able to metastasize. As to whether the particular neoplasm discussed in this section should be called a metastasizing leiomyoma or a low-grade leiomyosarcoma mimicking a leiomyoma depends on whether one wishes to designate tumors according to their morphology (in which case it would be a leiomyoma) or their behavior (in which case it would be a leiomyosarcoma). We favor the designation of low-grade leiomyosarcoma, once these bland tumors have been found to metastasize and thus declared their biological potential; in this regard, it may be opportune to quote here Julian Huxley—the famous biologist, zoologist, humanist, and popular writer—who, in his lecture on "Biological aspects of cancer," given at the Sloan Kettering Institute in 1955, stated when discussing the policy for designating lesions solely on the basis of their morphology: "This seems a regrettable example of specialist scholasticism. Cancer (malignancy) must be defined operatively in terms of what the tumor cells do, not what they look like; otherwise the term ceases to have biological meaning."[614]

Leiomyosarcoma

Clinical and Gross Features

Leiomyosarcomas occur in an older average age group than leiomyomas (median age, 54 years), although they can also occur in younger patients. Some of the epidemiologic findings in patients with leiomyosarcoma parallel those from studies in endometrial carcinoma and suggest a role for unopposed estrogen stimulation.[615] Some leiomyosarcomas are grossly similar to ordinary leiomyomas, but the majority are soft or fleshy, with necrotic or hemorrhagic areas and signs of invasiveness (Fig. 33.73).[616]

Microscopic Features

Microscopically, typical leiomyosarcomas are hypercellular, with nuclear atypia and pleomorphism, mitotically active (with some of the mitoses being atypical), and with areas of necrosis (Fig. 33.74).[617] Alas, not all leiomyosarcomas will exhibit simultaneously all of these features, whereas some leiomyomas can display one or several of them.[564] The relative importance of these criteria for the differential diagnosis between leiomyoma and leiomyosarcoma is the subject of a special section later.

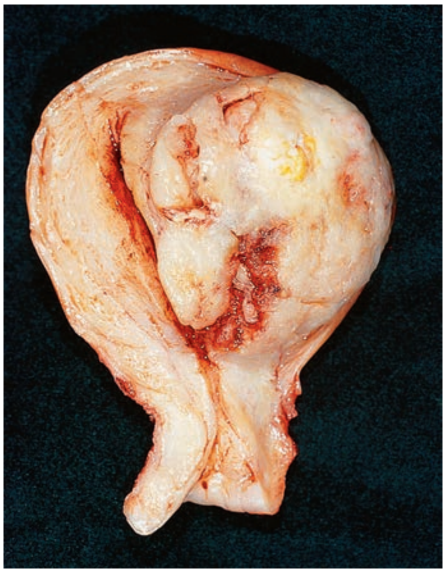


Figure 33.73 Leiomyosarcoma resulting in a large intramural and submucous mass. There are foci of hemorrhage and necrosis.

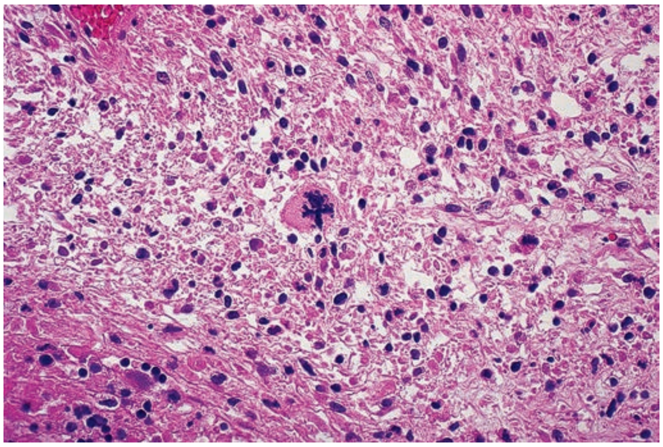


Figure 33.74 Leiomyosarcoma showing hypercellularity, pleomorphism, atypical mitoses, and necrosis.

Electron Microscopic, Immunohistochemical, and Molecular Genetic Features

Ultrastructurally and immunohistochemically, the features of leiomyosarcoma are those of smooth muscle cells.[619,620] There is consistent immunoreactivity for smooth and common muscle actin, desmin, calponin, h-caldesmon, and vimentin.[621] There is also common reactivity for low-molecular-weight keratin (as identified with CAM 5.2) and epithelial membrane antigen,[622] a feature that may lead to a mistaken interpretation, particularly if the tumor cells have an epithelioid appearance.[623] Estrogen and progesterone receptors are expressed, although with less degree of intensity than in leiomyomas.[624,625] The immunohistochemical profile of uterine leiomyosarcomas is somewhat different from that of leiomyosarcomas arising outside the female reproductive tract, probably due at least in part to the estrogen dependency of the former.[585,627]

At the molecular genetic level, there is no evidence of progression from leiomyoma to leiomyosarcoma.[456] Leiomyosarcomas are characterized by complex karyotypes comparable to their soft tissue counterparts. Breakpoint clusters have been mapped to 1q32 and 10q22.[456] In contrast to leiomyoma, there is commonly *TP53* mutation, which usually results in overexpression of p53.[625,629,630]

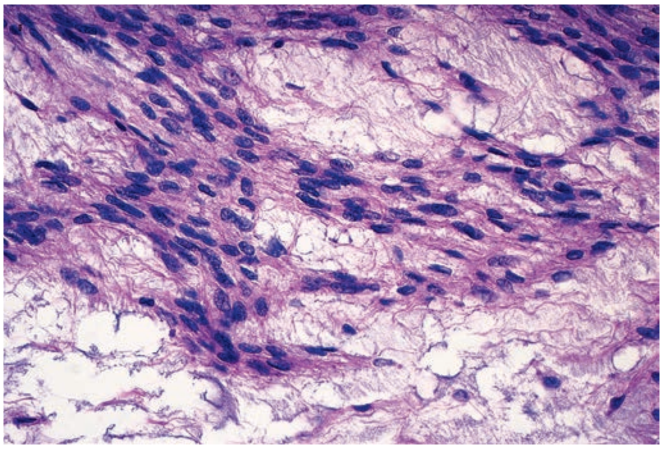


Figure 33.75 Uterine myxoid leiomyosarcoma. (Courtesy Dr. Robert E Scully, Boston.)

Leiomyosarcoma Variants

Epithelioid leiomyosarcoma are rare and must be distinguished from their benign counterpart (i.e. epithelioid leiomyoma).[631–633] General criteria apply (see earlier), such as marked atypia, larger size, infiltrating margins, mitotic activity, and presence of necrosis, and also absence of hyalinization.[631–633] Because of the rarity of epithelioid smooth muscle tumors, the criteria for distinction between benign and malignant are not as well developed as for the more common spindle cell smooth muscle tumors, and the designation of STUMP can be used for tumors with one or two concerning features, where an unequivocal diagnosis of leiomyosarcoma cannot be made. The differential diagnosis also includes endometrial stromal tumors, metastatic carcinoma,[634] and uterine gastrointestinal stromal tumor (GIST), which stain with GIST markers CD117 and DOG-1.[635]

Myxoid leiomyosarcoma can arise in the uterine wall, broad ligament, and other pelvic sites.[636] Grossly, it has a gelatinous appearance and deceptively well-circumscribed borders. Microscopically, however, it is invasive. The stroma is highly myxoid and the tumor cells are arranged as bundles of typical smooth muscle cells alternating with nondescript mesenchymal cells (Fig. 33.75). The main differential diagnosis (an important one) is with leiomyoma with hydropic degeneration. Regarding this differential, it is important to point out that the mitotic count criteria used for the usual leiomyosarcoma (see later) do not apply, in the sense that myxoid leiomyosarcomas tend to recur and metastasize whether mitoses are scanty (which is the usual situation) or numerous.[636,637]

Leiomyosarcoma with osteoclast-like giant cells occurs more frequently in the uterus than in any of the other places where malignant smooth muscle tumors can develop. The smooth muscle nature of the tumor cells—as confirmed immunohistochemically—distinguishes this entity from so-called "malignant giant cell tumor."[638]

Intravenous leiomyosarcomatosis, an exceptionally rare condition, can be viewed as the malignant counterpart of intravenous leiomyomatosis.[639]

Leiomyosarcoma with skeletal muscle differentiation is a vanishingly rare phenomenon similar to that sometimes seen in endometrial stromal sarcoma.[640]

Spread, Metastases, Treatment, and Prognosis

Uterine leiomyosarcoma usually spreads within the pelvis and in the form of distant metastases to the lung, bone, and other sites.[641] It is an aggressive neoplasm and most patients, even with Stage I tumors, die of disease; a curious phenomenon has occurred, attributable to more accurate diagnosis of benign leiomyoma variants that mimic leiomyosarcoma in current practice, that is, the outcomes of patients with stage I leiomyosarcoma in recent series appear worse than in the past.[642] Lymph node metastases are exceptional. The standard treatment is total abdominal hysterectomy with bilateral salpingo-oophorectomy. Prognostic factors include the following:

1. *Tumor stage.* Extension outside the confines of the uterus is a finding of ominous prognosis.[643] In one series of 20 patients in whom this occurred, there were no survivors beyond 29 months.[644]
2. *Tumor size.* This is a significant prognostic factor for tumors confined to the uterus.[645]
3. *Microscopic grade.* There is no accepted grading system for uterine leiomyosarcomas, and no consistent correlation has been found between survival and the histologic grade of the tumor. Specifically, the grading system used for sarcomas of the somatic soft tissue is not applicable.[646] Nonetheless, occasional leiomyosarcomas with more uniform nuclear features, lower mitotic rate, and apparently better outcomes do occur, [647] but we lack criteria to consistently recognize them in practice (except in retrospect).

Relationship Between Morphology and Behavior of Uterine Smooth Muscle Tumors

The majority of uterine smooth muscle tumors are readily classifiable into benign or malignant.[124,648] There are some lesions, however, for which that placement is very difficult, sometimes excruciatingly so.[650] The morphologic reasons for this, which at the same time represent the main criteria upon which to base a decision, are the following:

1. *Necrosis.* Two patterns of necrosis have been identified in smooth muscle tumors, respectively, named coagulative tumor cell necrosis and hyaline ischemic-type. In the former there is an abrupt transition between the necrotic and the viable cells. On low power, the typical appearance is that of a cuff of preserved tumor cells around large vessels surrounded by large expanses of necrotic tumor. On high power, two of the classic morphologic forms of nuclear necrosis (pyknosis and karyorrhexis) are evident. In hyaline/ischemic-type necrosis, there is a distinct zonal pattern reminiscent of an evolving infarct: a center of "bland" necrosis (i.e. one in which nuclear debris is difficult to see), a periphery of granulation tissue, and a layer of hyalinized collagen in between. Coagulative tumor cell necrosis, as defined previously, is currently regarded as the most important criterion of malignancy in these tumors. Unfortunately (but predictably) there is considerable interobserver variation in assessment of coagulative tumor cell necrosis.[651]
2. *Mitotic activity.* This remains another important criterion despite the admittedly imprecise fashion in which it is measured in terms of lack of standardization and poor reproducibility,[652–654] in the sense of being influenced by the thickness of the slide, microscope magnification factor, size of tumor cells, proportion of tumor cells to stroma, and observer criteria.[655] Regarding the latter, a common mistake among neophytes is to count the pyknotic nuclei often seen scattered around in smooth muscle tumors (whether from lymphocytes, mast cells, or smooth muscle cells) as mitotic figures. Another theoretical source of variation is the interval between excision and fixation, but this seems not to be important. Some practical measures can be taken to improve accuracy. One is to scan the sections for the *most active area*, do the mitotic count in 10 *consecutive fields* in that area, and repeat the procedure a minimum of *four times*. Another obvious measure is to sample the tumor adequately. Kempson[652] recommends a total of *at least 10 sections or one section for each centimeter of diameter, whichever is greater.* Note that this guideline applies to tumors with atypical gross or microscopic features, and not the majority of usual benign leiomyomas. HPF usually means the combination of a 10× eyepiece and a 40× objective. If the operator is using a 15× eyepiece and/or a 63× objective, adjustments should be made. The criteria for identifying mitotic figures should be strict. The members of the Multicenter Morphometric Mammary Carcinoma Project proposed the following:[656]
   1. The nuclear membrane must be absent, so cells must have passed the prophase.
   2. Clear, hairy extensions of nuclear material (condensed chromosomes) must be present, and clotted (beginning metaphase), in a plane (metaphase/anaphase), or in separate clots (telophase). Regular extensions with an empty central zone favor a nonmitosis.
3. *Atypia.* This refers to the combination of pleomorphism (meaning marked differences in size and shape) and nuclear hyperchromasia, and should already be evident on low-power examination. It is classified as focal or extensive, and graded (acknowledging the subjectivity of the exercise) as mild, moderate, or severe.
4. *Cellularity.* The term is self-explanatory and the determination just as subjective. This is one of the least important parameters in this exercise.
5. *Tumor borders*, that is, the relationship of the tumor with the surrounding myometrium.

The evaluation of these criteria, alone and in combination, allows a fairly accurate *but not infallible* prediction of tumor behavior. The points worth stressing are the following:

1. The weight of the morphologic factors, in order of significance, is coagulative tumor cell necrosis, high mitotic activity, pleomorphism, and cellularity (remembering that most leiomyosarcomas are evidently malignant at presentation, based on macroscopic evidence of invasiveness and metastasis, so that very detailed histomorphologic assessment is not necessary).
2. Tumors that are hypercellular but lack the other criteria are to be regarded as benign cellular leiomyomas.
3. Noninfiltrative tumors with atypia (even if marked and diffuse) should not be regarded as malignant if they lack coagulative tumor cell necrosis and mitotic activity is less than 10/10 HPF. Rather, they belong to the category of *leiomyoma with bizarre nuclei* if mitoses are rare (<2/10 HPF) and to the category of STUMP if mitotic activity is 2–10/10 HPF.
4. Tumors with increased mitotic activity (up to 15 mitoses per 10 HPF) but lacking coagulative tumor cell necrosis and atypia are to be regarded as *mitotically active leiomyomas*.
5. Tumors with coagulative necrosis and diffuse atypia and/or increased mitotic activity (>10 per 10 HPF) should be regarded as leiomyosarcomas.
6. Tumors with coagulative necrosis but neither atypia nor increased mitotic activity should be diagnosed as STUMP.
7. Tumors with diffuse moderate-to-severe atypia *and* 10 or more mitoses per 10 HPF should be called leiomyosarcoma even if they lack coagulative tumor cell necrosis.

These recommendations are primarily based on the careful and painstaking work done by Richard Kempson and colleagues over a 35-year period.[648,655,657–661] Some modifications are made, based on the 2014 WHO guidelines,[662] and this approach to diagnosis is illustrated in a simplified form for the benefit of the reader in Table 33.2. Although Kempson and colleagues did not propose a "STUMP"

Table 33.2 Criteria and diagnostic terms for uterine smooth muscle tumors

COAGULATIVE TUMOR CELL NECROSIS	MITOTIC COUNT PER 10 HPF	ATYPIA		DIAGNOSIS
Present	Greater than 10	Moderate to severe (focal or diffuse)		Leiomyosarcoma
		None to mild		Leiomyosarcoma
	Equal to or less than 10	Moderate to severe (focal or diffuse)		Leiomyosarcoma
		None to mild		STUMP
Absent	Greater than 10	Moderate to severe	Diffuse	Leiomyosarcoma
			Focal	STUMP
		None to mild		Mitotically active leiomyoma (up to 15 mitoses/10 HPF are allowed)
	1 to 10	Moderate to severe	Diffuse	STUMP
			Focal	STUMP
		None to mild		Mitotically Active Leiomyoma

Data from Kempson RL, Hendrickson MR. Smooth muscle, endometrial stromal, and mixed Mullerian tumors of the uterus. *Mod Pathol*. 2000;13:328–342.

category, it has been retained in this table, in keeping with the WHO classification.[662]

In our opinion, one would serve the patient and the clinician better (and would also be closer to expressing the truth) by doing away with the traditional binary classification of these tumors into benign and malignant (i.e. leiomyoma versus leiomyosarcoma), which is improved only slightly by the addition of a STUMP category, and by switching to a nomenclature that would simply identify these neoplasms as smooth muscle tumors, followed by an estimation (ideally expressed in percentages) of the probability of the tumor recurring or metastasizing, based on a careful evaluation of all the parameters discussed in this section and any others that may be found of help in this regard. Until and unless such a radical change in nosology takes place, and as long as we subject ourselves to the current Manicheist approach, the above recommendations will have to do.

Two additional comments are in order. These considerations have been devised for the conventional type of uterine smooth muscle tumor and cannot be applied unchanged to the variants. For instance, myxoid leiomyosarcoma is to be diagnosed as such even if in most cases it lacks coagulative necrosis, increased mitotic activity, and severe atypia.

The other comment applies to the hope that the abundant information that is being obtained regarding the genotypic features of these tumors will provide assistance to the pathologist in terms of an accurate prognostic assessment and a precise therapeutic recommendation. The most promising modality to date is comparative genomic hybridization with determination of a genomic index; this can separate leiomyomas, with minimal genomic perturbation, from leiomyosarcomas, and identifies STUMPs with high versus low risk of recurrence but is some ways off from being sufficiently validated for everyday use.[663] It is fair to say that the decision to place a uterine smooth muscle tumor into a given prognostic category remains for now largely dependent on the time-honored morphologic criteria.

PEComa

Perivascular epithelioid cell tumors (PEComas) are tumors showing both melanocytic and smooth muscle differentiation.[664] They occur at non-gynecologic sites, and their recognition in the uterus was delayed because of their rarity and the overwhelming number and variety of uterine smooth muscle tumors; undoubtedly in the past these were diagnosed as smooth muscle tumors, especially of the epithelioid variant. Some of these tumors are associated with pelvic lymphangiomyomatosis and/or have developed in patients with tuberous sclerosis.[665-668] They can be benign or malignant; because there are few reported cases, the criteria for diagnosis of malignancy are not well established.[664,669] The uterine corpus is the most common location of PEComas of the female reproductive organs; grossly they resemble smooth muscle tumors. Microscopically they consist of epithelioid cells or a mixture of epithelioid and spindle cells. Conspicuous sclerosis is present in some tumors. Necrosis is present in almost half, as is significant nuclear atypia. Mitotic activity is variable, from undetectable to brisk. The tumor cells consistently stain for HMB-45, with a minority of case showing immunoreactivity for Melan-A or MiTF.[664,670] Smooth muscle markers (smooth muscle actin, desmin, caldesmon) are expressed in approximately 2/3 of cases.[664] Features associated with malignancy include size greater than 5 cm, infiltrative margin, high nuclear grade, increased cellularity, mitotic rate >1/50 HPF, vascular invasion, and necrosis.[669] The absence of ALL these features is associated with benign behavior, while it has been suggested that the presence of one feature should lead to designation as "uncertain malignant potential," and two or more of these features is associated with malignant behavior in most cases.[664,669]

There are case reports of PEComatosis, with multiple PEComas variously involving the female reproductive organs, bowel wall, omentum, and lymph nodes.[671]

Both syndromic (tuberous sclerosis complex) and sporadic PEComas are associated with TSC1 or TSC2 inactivation.[672] TFE-3 translocations have been identified in a subset of PEComas.[560,673]

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor is similar to PEComa in that it can occur at many sites in the body but when it was present in the uterus it has often been mistaken for a smooth muscle tumor. Inflammatory myofibroblastic tumors of the uterus can occur at any age, including in childhood.[675–677] They can appear ill-defined grossly but tend to resemble leiomyomas. The microscopic appearance is identical to inflammatory myofibroblastic tumors occurring elsewhere in the body; the plump spindle cells can be separated by edematous stroma, grown in fascicles, or there can be stromal hyalinization (Fig. 33.76).[677] The myxoid areas can raise the differential diagnosis of myxoid leiomyosarcoma or a myxoid pattern of endometrial stromal sarcoma, such as the subtype with *BCOR* alteration.[676] A

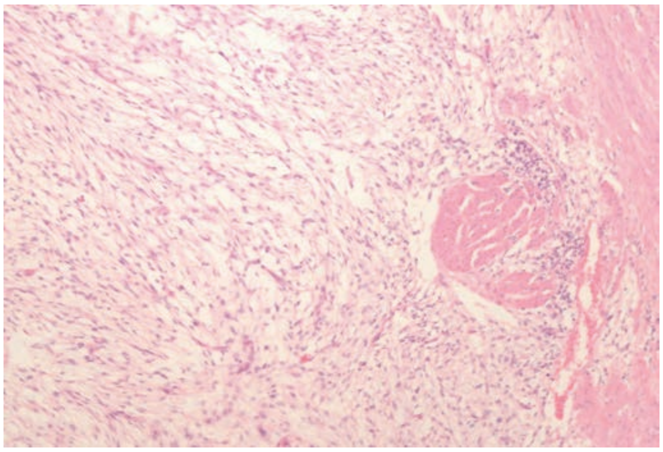


Figure 33.76 Inflammatory myofibroblastic tumor.

mononuclear inflammatory infiltrate rich in plasma cells is invariably present but may be sparse in areas. ALK immunoreactivity is an important diagnostic adjunct, distinguishing inflammatory myofibroblastic tumor from smooth muscle neoplasms.[677] Some have pursued an aggressive course.[676]

Gestational Trophoblastic Neoplasia

There is a group of diseases related to normal or abnormal gestation that have as a common denominator the proliferation of trophoblast and that are generically designated as *(gestational) trophoblastic neoplasia*. The individual disorders differ remarkably in appearance and clinical significance. The major ones are hydatidiform mole (complete, partial, or invasive), placental site trophoblastic tumor, and choriocarcinoma.[678] The pathogenesis of these remains poorly understood, but genomic imprinting is believed to play a key role in the formation of hydatidiform moles.[679-681]

Hydatidiform Mole

In hydatidiform moles, the trophoblastic proliferation is associated with swelling of the villi. They are subdivided into complete and partial types, and either type can be invasive.

Complete Mole

Complete hydatidiform mole is caused by abnormal gametogenesis and fertilization. The nuclei of the trophoblastic cells in this disease contain only paternal chromosomes and are, therefore, androgenetic in origin.[682,683] In most cases the chromosomal number is normal; 85% of cases are 46,XX and 15% are 46,XY. In a minority of cases, the DNA pattern is tetraploid, these generally occurring in an older age group.[656]

There is a striking geographic variation in the frequency of complete mole. In Southeast Asia, the reported incidence is at least 4 to 5 times greater than in the United States.[684,685] Yet higher incidences have been reported from Mexico (1 : 200), the Philippines (1 : 173), India (1 : 160), Taiwan (1 : 125), and Indonesia (1 : 82).[686] A history of previous term birth reduces the risk of molar pregnancy, whereas a history of a previous mole greatly increases the probability of developing another.[685,687,688] "Repetitive" moles are usually of complete type, but they can be of partial type, or a complete mole may be followed by a partial mole.[689]

Clinically, the uterus involved by a complete mole is disproportionately large for the stage of pregnancy.[690] Serum hCG levels continue to rise after the 14th week, as opposed to the drop typically seen in the course of normal gestation. Evidence of toxemia of pregnancy (hypertension, edema, albuminuria) is frequently found, and this typically occurs during the early stages of the pregnancy. Exceptionally, hyperthyroidism develops as a result of a thyroid stimulator secreted by the molar tissue, perhaps residing in the hCG molecule itself.[691–693] At the time of the medical consultation there may be vaginal bleeding, a sign that the mole has begun to abort spontaneously.

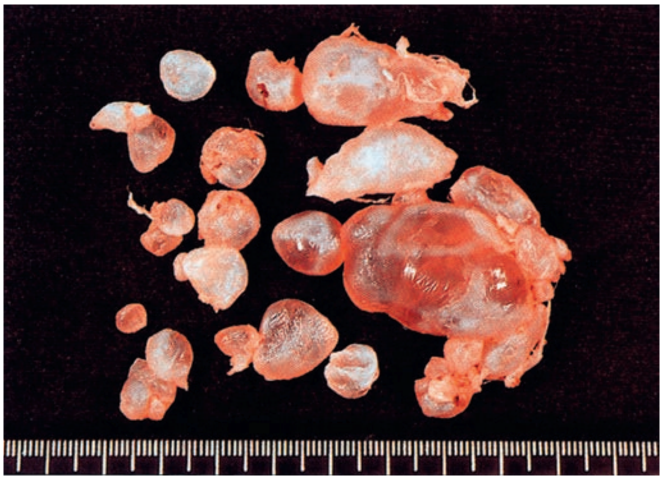


Figure 33.77 **Complete Mole.** All villi are markedly swollen. (Courtesy Dr. Pedro J Grases Galofrè; from Grases Galofrè PJ. *Patologia ginecològica. Bases para el diagnòstico morfològico*. Barcelona: Masson; 2002.)

Grossly, the complete mole has been typically described as a "bunch of grapes," with all or nearly all the villi showing hydropic degeneration. The individual vesicles measure anywhere from 1 to 30 mm in diameter, and the total weight is usually over 200 g. In a hysterectomy specimen, these swollen villi are seen to fill and distend the uterus (Fig. 33.77). Characteristically, there are no identifiable embryo, cord, or amniotic membranes. The exceptional cases of bona fide complete mole in which an embryo is present almost invariably represent a twin gestation.[694,695]

Microscopically, the two constant features of a complete mole are *trophoblastic hyperplasia* and *vesicular swelling*, the latter probably representing a secondary phenomenon. The severity of the changes varies considerably from case to case and from villus to villus and may be difficult to appreciate in very early cases, as evidenced by the high degree of interobserver and intraobserver diagnostic variability.[696–698] Some of the villi are surrounded by an attenuated layer of degenerating trophoblast. In others, the trophoblast forms large hyperplastic sheets of cells (Fig. 33.78). The distended core of the villus is traversed by widely separated, broken strands of fibrillar material ("cistern" formation). Vessels seem absent or very scanty in hematoxylin–eosin-stained sections, even though they do not seem very diminished in number in CD34-stained preparations.[699] The stromal changes of molar villi, which include stromal mucin and stromal nuclear debris (apoptosis), appear very early and represent a diagnostic clue.[700–702] The trophoblastic hyperplasia characteristically has a circumferential but haphazard arrangement around the individual villi, as opposed to the polar proliferation seen in normal first-trimester villi. The plexiform pattern of intermixed syncytiotrophoblast and cytotrophoblast seen in choriocarcinoma does not occur. Trophoblastic hyperplasia with atypia also occurs at the implantation site, to a much greater degree than in hydropic villi of abortion or partial moles.[703]

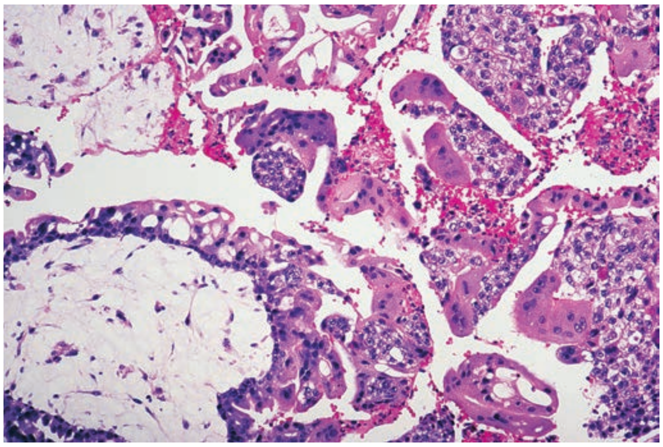


Figure 33.78 Complete mole showing large villi with stromal edema and marked trophoblastic proliferation.

Ultrastructurally, the molar trophoblast closely resembles that seen during the first trimester of a normal pregnancy.[704]

Immunohistochemically, hCG is widely distributed and PLAP is patchily distributed in the molar syncytiotrophoblast regardless of gestational age, whereas hPL tends to increase with increased gestational age.[705,706] Both the α- and β-subunits of inhibin are evident in the molar syncytiotrophoblast.[707,708] A very useful marker for the differential diagnosis of complete mole is p57^{kip2} protein, a cell cycle inhibitor and tumor suppressor encoded by a strongly paternally imprinted gene. It is expressed in the cytotrophoblast and villous mesenchyme of normal pregnancy, spontaneous abortions, and partial moles but absent or very markedly decreased in complete moles because both copies of the *TP57* gene are of paternal origin.[709–712]

By flow cytometry, complete moles are most commonly diploid, with the non-diploid being tetraploid in a most instances.[713] Heterozygous (dispermic) moles, including dispermic heterozygous XY moles, are associated with a higher incidence of persistent trophoblastic disease than homozygous (monospermic) moles.[714]

The initial therapy of complete mole consists of evacuation of the uterus by curettage.[715] This is followed by sequential quantitative determination of the β-subunit of hCG.[716,717] The standard recommendation has been to measure the serum level of hCG at 10, 20, 30, 45, and 60 days after termination of the molar gestation. In approximately 80% of cases, normal levels will be reached by day 60. If there is rising titer between day 45 and day 60 or the level is still elevated by day 60, chemotherapy is administered; this is necessary in approximately 20% of cases.[718] With this approach, the cure rate is close to 100%.[719] Unfortunately, the use of etoposide has been found to be associated with an increased risk of development of second tumors.[720]

Other authors recommend the administration of chemotherapy to those patients who have a plateau of three high values of hCG over a 2-week period after evacuation of the mole (approximately 20%–30% of cases). Still others recommend waiting for 4 weeks or even 2 months before initiating chemotherapy, especially if the hCG levels are low.[721]

In a series of 738 patients with mole, spontaneous regression occurred in 81%. Of the remaining patients, 17% developed an invasive mole, and 2% developed choriocarcinoma.[722] The presence of villi or atypical trophoblast following the evacuation of a molar pregnancy indicates "persistent trophoblastic disease," but the decision of whether to give chemotherapy or not still largely depends on the hCG levels.

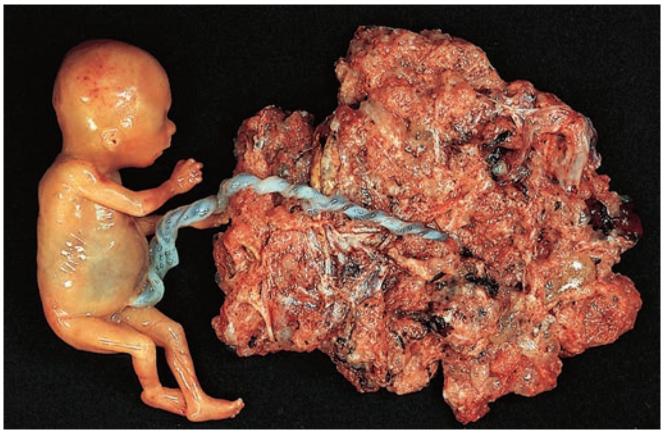


Figure 33.79 Partial Mole With Attached Fetus. The fetus showed no abnormality and was connected to the mole by a normal umbilical cord. (Courtesy Dr. Pedro J Grases Galofré; from Grases Galofré PJ. *Patología ginecológica. Bases para el diagnóstico morfológico*. Barcelona: Masson; 2002.)

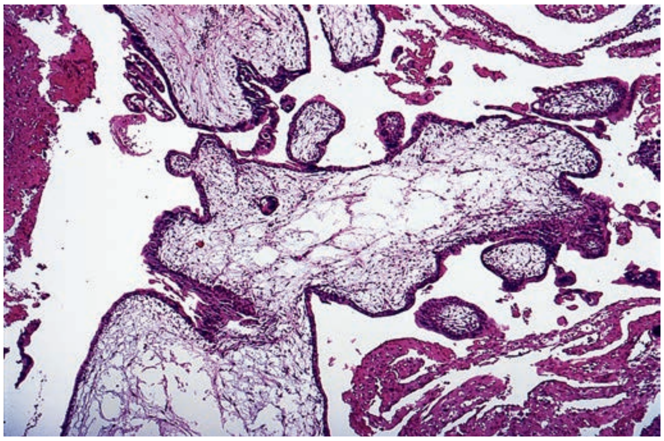


Figure 33.80 Partial mole showing scalloping of villi and isolated trophoblastic cells embedded in the stroma.

Partial Mole

Approximately 15%–35% of all moles are of the partial type. In contrast to complete mole, the condition is often associated with the presence of an embryo, although this is usually abnormal ("blighted ovum"). The volume of placental tissue is relatively normal, and the grossly vesicular villi are mixed with normal-appearing ones (Fig. 33.79). The former often show focal edema leading to central "cisternal" formation and stromal inclusions of trophoblast (Fig. 33.80). Many of the villi have an irregular, scalloped outline and contain vessels with fetal (nucleated) red blood cells. Fibrosis of the villous stroma is common. Trophoblastic proliferation is present, although generally to less degree than in complete mole; cytoplasmic vacuolization of the syncytiotrophoblast is prominent.[723]

Most partial moles are triploid (69,XXX or 69,XXY) and a few show trisomy 16.[724–726] The extra material is of paternal derivation (so-called "diandric triploidy").[727]

Because of the generally small size of the lesion, the uterine size is nearly always small or appropriate for the gestational age. Serum hCG levels—although elevated—tend to be relatively low, and the ovarian theca-lutein cysts that commonly accompany complete moles do not occur.[728] The risk for the development of choriocarcinoma following a partial mole is very low, but a few well-documented cases are on record.[729,730] Furthermore, some series document a 5%–10% incidence of persistent disease (lower in those evacuated early),[731] indicating that follow-up of these patients is mandatory.[732–734] Some of the recurrences have been in the form of invasive mole[735–737] and some in the form of lung metastases.[738]

As already pointed out, not all placentas of triploid conceptuses show partial molar transformation; some (perhaps the majority) have a normal morphologic appearance.[739] The triploid fetuses in both groups tend to die at about 8 weeks menstrual age.[740]

Partial moles should be distinguished on one hand from complete moles and on the other from the hydropic villi seen in 15%–40% of spontaneous abortions and with rare conditions such as placental stem villous hydrops, mesenchymal dysplasia, and Beckwith–Wiedemann syndrome.[741] As noted previously, the pattern of p57 immunostaining, with expression in cytotrophoblast and villous mesenchyme, serves to distinguish between complete and partial mole but is not helpful in the distinction between partial mole and hydropic abortion. With regard to the differential diagnosis between partial mole and hydropic abortion, in the latter gross villous swelling and cistern formation are not present. As already stated, the villous trophoblast in spontaneous abortions either is attenuated or—if proliferating—has a polar distribution. Furthermore, trophoblastic atypia is absent or minimal. Flow cytometry studies are of great assistance in the evaluation of this problem, with triploidy favoring a diagnosis of partial mole, being mindful that triploid spontaneous abortions do occur, but lack histologic features of partial mole.[727,732,742] Flow cytometry for ploidy assessment is not widely available and FISH for HER2, which is, can serve as a surrogate test, as trisomy for chromosome 17, as determined with the HER2 and centromeric probes used for breast and gastric cancer HER2 FISH, is an indicator of triploidy.[743] The "gold standard," however, in the diagnosis of mole is genotypic analysis using the technology developed for DNA fingerprinting/forensic identification, as it allows determination of copy number and parent of origin of the DNA, improving diagnostic accuracy.[744] This approach is not widely available and is relatively expensive, so the diagnosis of molar pregnancy is still based largely on routine histology with liberal use of p57 immunostaining.

Invasive Mole

The term *invasive mole* refers to a hydatidiform mole (nearly always of the complete type but occasionally of the partial type) in which villi penetrate deeply the myometrium and/or its blood vessels (Figs. 33.81–33.83).[745,746] This phenomenon, which occurs in 16% of all complete moles, is an exaggerated expression of the capacity of normal trophoblast for invasion, a necessary property for implantation.

The myometrial permeation in invasive mole may be extensive and may lead to persistent hemorrhage, but the serosa is usually intact. However, uterine perforation may occur. The vascular invasion may result in trophoblastic nodules in sites outside the uterus, such as the vagina, lung, brain, and spinal cord.[747,748] The lung nodules have a characteristic radiographic appearance[749,750]; they continue to produce hCG and have a similar tendency for hemorrhagic complications. The clinical manifestations depend on the site involved: a sizable mass in the lung may regress spontaneously without ever causing symptoms, whereas a deposit in the brain may produce fatal hemorrhage.[751,752]

It should be mentioned that invasive mole is distinguished from the usual mole by its invasiveness and from choriocarcinoma by the presence of villi, which are also present in the "metastatic" foci. The degree of trophoblastic proliferation in invasive mole does not differ significantly from that of its ordinary counterpart. Patients

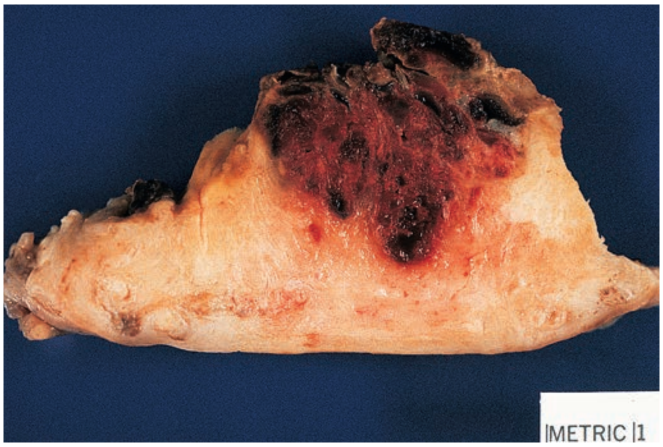


Figure 33.81 **Gross Appearance of Invasive Mole.** A hemorrhagic mass has permeated half of the thickness of the myometrial wall.

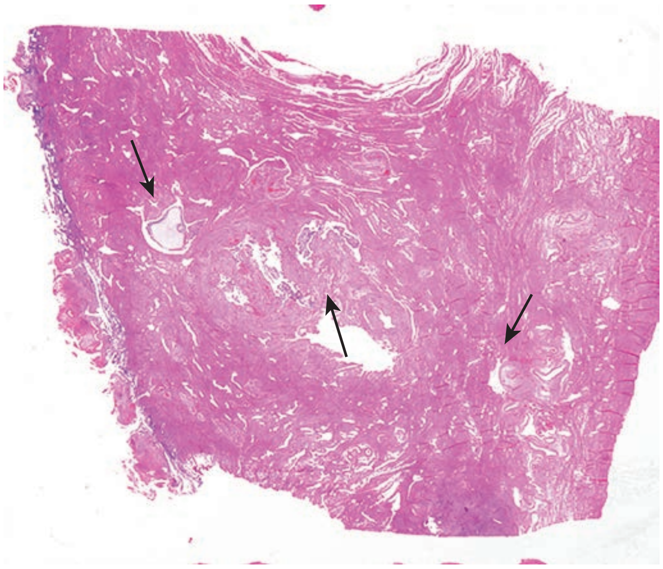


Figure 33.82 **Whole-Mount View of Invasive Mole.** Abnormal villi are seen permeating the thickened myometrium *(arrows)*.

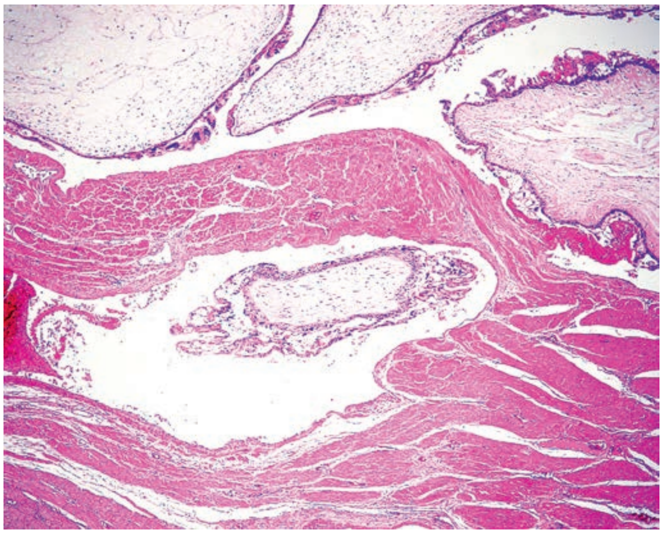


Figure 33.83 Hydropic villi covered by proliferating trophoblast are seen permeating the myometrium in this invasive mole.

with invasive mole are primarily treated with chemotherapy, but hysterectomy may be indicated in some circumstances.[746,753]

Choriocarcinoma

Choriocarcinoma, when untreated, is the most aggressive form of gestational trophoblastic neoplasia. Most cases occur following a complete hydatidiform mole; consequently, this malignant tumor is more common in areas of the world in which hydatidiform mole is prevalent. It has been estimated that 1%–2% of complete moles are followed by choriocarcinoma.[754]

Choriocarcinoma can also be preceded by a partial mole (a very unusual event), ectopic pregnancy, nonmolar intrauterine abortion, or term pregnancy.[755–757] In the latter instance, which is exceptionally rare, the tumor may appear as one or more masses in an otherwise normal placenta or develop following the delivery.[758–760] In addition, cases of "in-situ" choriocarcinoma arising from the trophoblast of stem villi in the first trimester of pregnancy have been described.[761]

In cases of choriocarcinoma following abortion—whether molar or not—the latent period is almost always less than 1 year, although it can be considerably longer ("latent choriocarcinoma").[762] At the time of the diagnosis of the malignancy, the average age of the patient is 29 years.

Grossly, choriocarcinoma characteristically forms soft, dark red, hemorrhagic, round nodular tumor masses (Fig. 33.84). Microscopically, the tumor is composed of clusters of cytotrophoblast separated by streaming masses of syncytiotrophoblast, resulting in a characteristic dimorphic plexiform pattern (Fig. 33.85).[763] Hemorrhage and necrosis are usually present but have no real diagnostic significance, since they are also commonly found in spontaneous abortions. Villi are characteristically absent; as a matter of fact, their presence is said to rule out the diagnosis of choriocarcinoma no matter how atypical the trophoblastic cells may be.[764]

Immunohistochemically, choriocarcinoma cells are positive for hCG and keratin. There may also be reactivity for hPL, SP1, and CEA.[765] There can be a minor component of intermediate trophoblastic cells immunoreactive for hPL, CD146 (Mel-CAM), HLA-G, and inhibin.

The natural history of untreated choriocarcinoma is characterized by the development of early hematogenous metastases, the most common sites being the lung, brain, liver, kidney, and bowel.[766–768] They can be clinically solitary, may occur in the most unusual places, and often present with massive hemorrhage.[769] Interestingly, the fetus is rarely involved, even in cases of widespread metastatic disease.[770] Residual tumor in the uterus of patients dying of disseminated choriocarcinoma may be inconspicuous or altogether absent.[771]

Many of the morphologic changes seen in other organs in patients with choriocarcinoma are the result of increased secretion of hCG and other hormones by the tumor cells. These include hyperplasia of endocervical glands, decidual reaction (both endometrial and ectopic), Arias-Stella phenomenon, bilateral enlargement of the ovaries by theca-lutein cysts ("hyperreactio luteinalis"), and hyperplasia of mammary lobules. The detection of ovarian theca-lutein cysts long after a case of choriocarcinoma has been treated is usually a sign of persistent disease.[772] In the endometrial decidual reaction of patients with choriocarcinoma, the spiral arterioles fail to develop as they do in the normal cycle, the appearance of the mucosa being similar to that seen after the administration of progestogens.[771]

The evolution of the treatment of choriocarcinoma (and of gestational trophoblastic neoplasia in general) is one of the greatest success stories in medical oncology.[773] When treated by surgery alone, the cure rate was only 40% for tumors apparently restricted to the uterus and less than 20% for those accompanied by metastases.[774] With the use of chemotherapy, the survival rate is close to 100% for cases restricted to the uterus and approximately 83% for patients with metastatic disease.[775,776] Low- and high-risk patient groups have

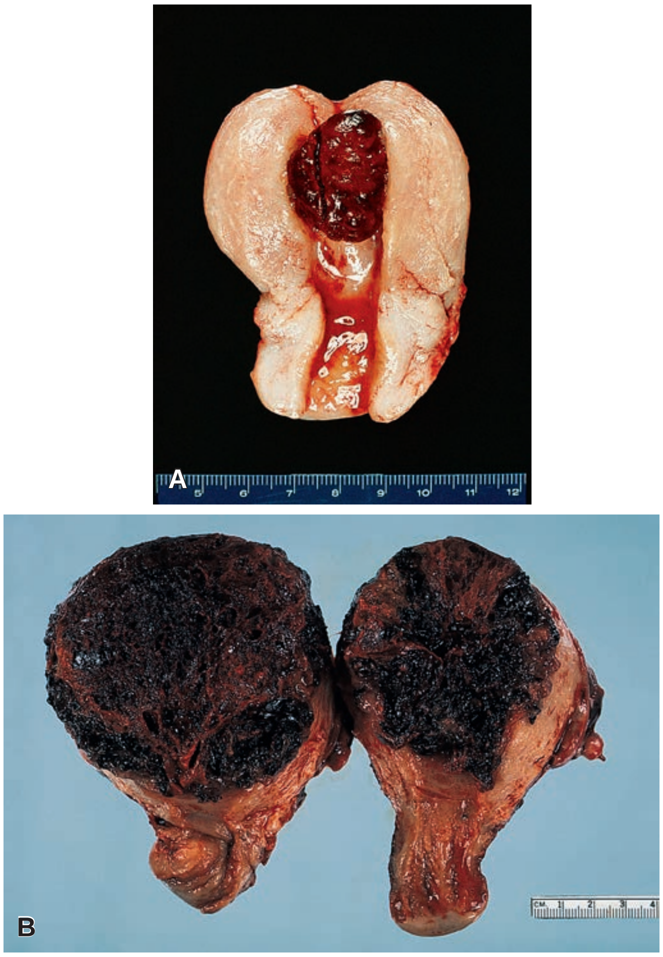


Figure 33.84 **A** and **B,** Uterine choriocarcinoma showing typical highly hemorrhagic appearance.

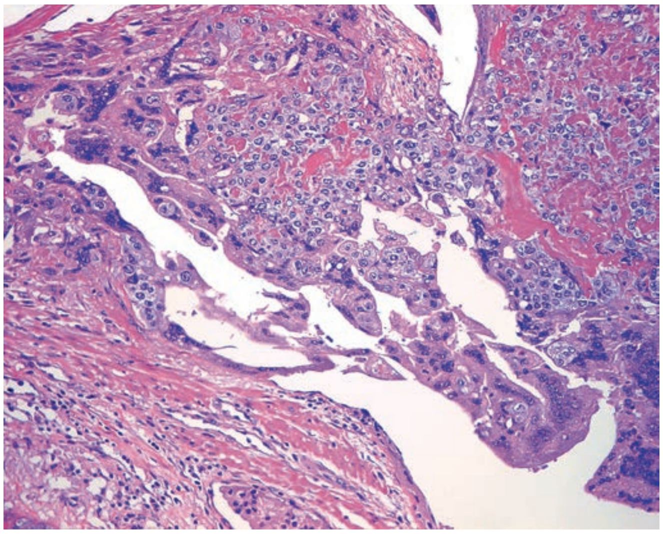


Figure 33.85 Intimate admixture of syncytiotrophoblast and cytotrophoblast in choriocarcinoma.

Table 33.3 FIGO/WHO Prognostic Index Score for gestational trophoblastic neoplasia

	SCORE[a]			
PROGNOSTIC FACTOR	**0**	**1**	**2**	**4**
Age (years)	≤39	>39	—	—
Antecedent pregnancy	Hydatidiform mole	Abortion	Term	—
Interval (months)[b]	4	4–6	7–12	>12
β-hCG (IU/L)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Largest tumor, including uterine tumor	<3 cm	3–5 cm	>5 cm	–
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	—	1–4	5–8	>8
Prior chemotherapy	—	—	Single drug	Two or more drugs

[a] The total score for a patient is obtained by adding the individual scores for each prognostic factor: low risk, 0–6; high risk, ≥7.
[b] Interval is time between end of antecedent pregnancy and start of chemotherapy.
From Kurman RJ, Carcangiu ML, Herrington CS, Young RH, eds. *WHO Classification of Tumors of the Female Reproductive Organs*. Lyon: IARC; 2014.

been identified on the basis of location of metastases, hCG, and duration of the disease (Table 33.3).[777]

In most cases the uterus can be retained. Hysterectomy is performed in those patients in whom preservation of the reproductive function is not desired and/or who are unresponsive to chemotherapy alone. Surgery also remains useful in controlling life-threatening hemorrhage from metastatic lesions.[778,779]

The importance of early diagnosis, prompt institution of therapy, and monitoring of the effects of treatment with sequential quantitative determination of hCG production cannot be overemphasized. In regard to the latter, it should be mentioned that hCG secretion is by no means restricted to gestational choriocarcinomas. It can also occur in nongestational choriocarcinoma; other ovarian and testicular germ cell tumors; melanoma; malignant lymphoma; and carcinomas of the esophagus, stomach, pancreas, kidney, liver, lung, urinary bladder, uterus, adrenal gland, breast, and other sites. A feature common to many of these tumors is the presence of tumor giant cells shown to contain hCG by immunocytochemical techniques.[780]

Genetic studies using the same technique used to aid in diagnosis of molar pregnancy, described previously, and distinguish gestational from nongestational choriocarcinoma by identification of paternal DNA.[744]

Placental Site Trophoblastic Tumor and Related Lesions of Intermediate Trophoblast

Placental site trophoblastic tumor is a rare form of trophoblastic disease.[782–784] About 75% of cases follow a normal pregnancy, with only 5% of the reported patients having had a preceding molar pregnancy.[785] A paternally derived X chromosome and the absence of a Y chromosome may be necessary for its formation, consistent with an origin from the trophectoderm of a female conceptum.[786,787] It presents grossly as a myometrial mass that can be well localized or ill defined (Fig. 33.86A). Hemorrhage is not as conspicuous as in invasive mole or choriocarcinoma. The uterine penetration may be deep, and perforation may result, either spontaneously or following curettage.

Microscopically, large trophoblastic cells with abundant eosinophilic cytoplasm and nuclear pleomorphism are seen invading the myometrium and vessel lumina (see Fig. 33.86B). The morphologic, ultrastructural, and immunohistochemical features of these cells correspond to those of intermediate trophoblast.[788–791] As such, the immunoreactivity for hPL is strong and widespread, whereas that for hCG tends to be focal.[792,793] There is also positivity for keratin, CD66a (CEACAM1), CD146 (Mel-CAM), pregnancy-associated major basic protein, HLA-G, and inhibin.[794–796] The DNA pattern, as determined by flow cytometry, is usually diploid,[797,798] and this seems to also be the case in the rare examples with malignant behavior.[799] The Ki-67 labeling index is higher than in exaggerated placental site reaction but lower than in choriocarcinoma.[800] There is no expression of p63, an useful feature in the differential diagnosis with epithelioid trophoblastic tumor (see later).[801]

Although this condition was initially considered to be an exuberant form of syncytial endometritis,[782] additional experience has shown that it is instead a neoplastic process with a 10%–20% mortality rate if not treated properly.[802] Some cases have resulted in widespread metastases;[797,803] these have generally shown a high mitotic count in the primary tumor, extensive necrosis, and/or a preponderance of cells with clear cytoplasm.[783]

Serum hCG levels in placental site trophoblastic tumor are usually not as high as in choriocarcinoma and may not accurately reflect the extent of the disease. Sometimes the tumor is totally resistant to chemotherapy.[804,805] A distinctive renal glomerular lesion accompanied by proteinuria and hematuria and characterized by occlusive eosinophilic deposits in the glomerular capillary lumina has been observed in connection with this neoplasm.[806]

The differential diagnosis of placental site trophoblastic tumor includes other gestational trophoblastic diseases, as well as nonneoplastic placental proliferations of intermediate trophoblast, especially placental site nodule. In contrast to placental site nodule, placental site trophoblastic tumor shows confluent growth of intermediate trophoblast and Ki-67 labeling index of greater than 10%. The distinction with choriocarcinoma is made because of a lack of a dimorphic population of cytotrophoblast and syncytiotrophoblast (although scattered multinucleated cells may be present), lack or paucity of hemorrhage, and the presence of an interdigitating pattern of muscle invasion.

Epithelioid Trophoblastic Tumor

Epithelioid trophoblastic tumor, the latest entry into the gestational trophoblastic disease family, was originally described as a peculiar

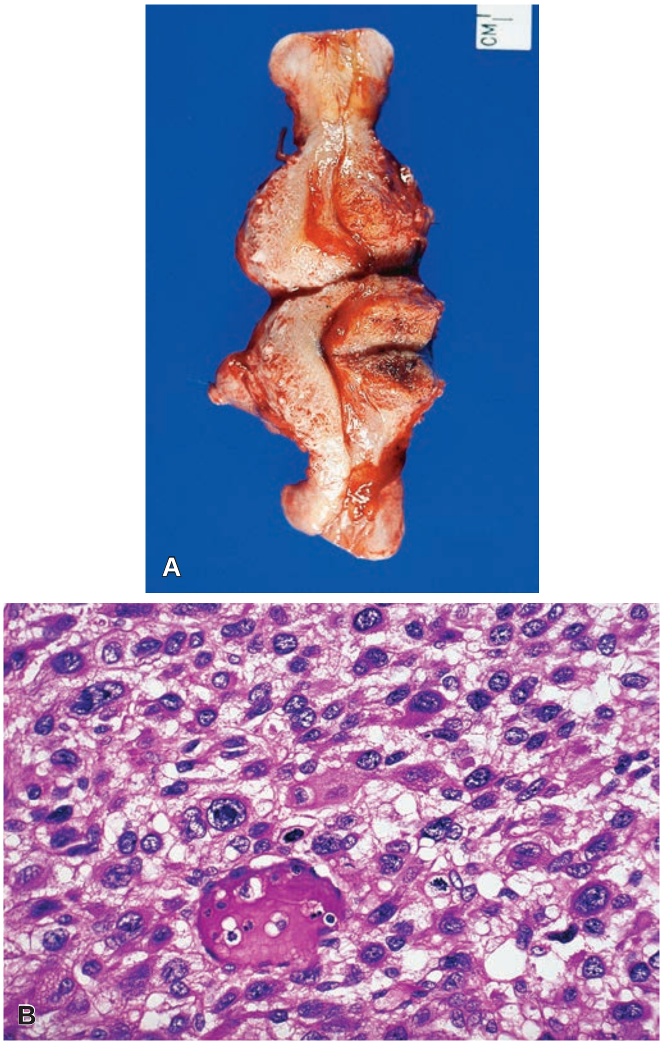


Figure 33.86 **A** and **B,** Placental site trophoblastic tumor. **A,** Gross appearance. A solid hemorrhagic nodule is seen distending the myometrium and protruding into the endometrial cavity. **B,** Microscopic appearance. Medium-sized cells of intermediate trophoblastic type are seen growing in a diffuse fashion into the myometrium. The biphasic pattern resulting from the admixture of cytotrophoblast and syncytiotrophoblast, which is typical of choriocarcinoma, is absent.

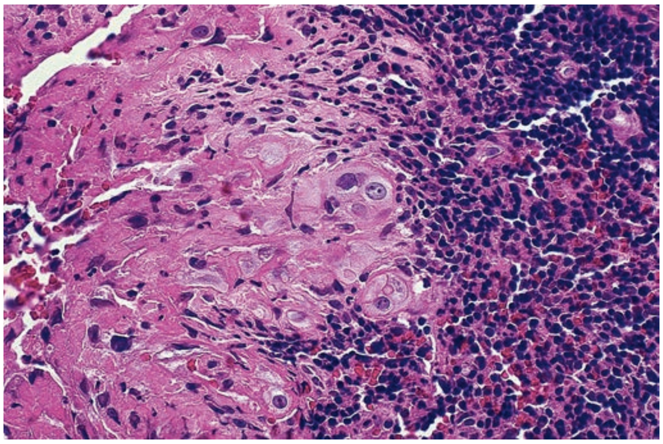


Figure 33.87 **Epithelioid Trophoblastic Tumor.** The microscopic appearance closely simulates carcinoma of either squamous or glassy cell type.

change in the metastatic foci of choriocarcinoma surgically excised following chemotherapy[807] but is now known to also occur de novo. Like the other members of the family, it usually occurs in the reproductive age group (although it can be seen after menopause),[808] and it presents with abnormal vaginal bleeding. The primary tumor most commonly occurs in the endomyometrium but can sometimes be centered in the uterine cervix,[809] develop outside the uterus in places such as the broad ligament,[810] or even present as a primary lung tumor, simulating microscopically squamous and pleomorphic carcinomas of this organ.[811] hCG levels are usually elevated. Grossly, it is solid and cystic, discrete, and hemorrhagic. Microscopically, it is composed of a relatively uniform population of intermediate trophoblastic cells forming nests and solid masses. Necrosis is extensive, and there is a hyaline matrix with a geographic configuration (Fig. 33.87). The appearance closely simulates that of a carcinoma. Immunohistochemically, there is diffuse reactivity for keratin, α-inhibin, EMA, p63, HLA-G, and E-cadherin but only focal reactivity for hPL, hCG, PLAP, and CD116 (Mel-CAM).[812] Positivity for cyclin E helps in the differential diagnosis with placental site trophoblastic tumor, and lack of reactivity for p16 is useful in the differential diagnosis with cervical and other types of carcinoma.[813] Shih and Kurman[814] believe that the tumor is composed of chorion laeve-type intermediate trophoblast. Molecular genetic analysis has confirmed its trophoblastic origin by demonstrating a Y-chromosomal locus and/or new (paternal) alleles not present in the adjacent normal uterine tissue.[815] It behaves as a malignant tumor, with metastases to lung and other sites.[814]

Tumorlike Conditions of Intermediate Trophoblast. Nonneoplastic proliferations of intermediate trophoblast that can create serious problems in the differential diagnosis with malignant trophoblastic tumors are exaggerated placental site reaction, placental site nodule, and placental site plaque.[816]

Exaggerated placental site reaction was called syncytial endometritis in the past, but this was a double misnomer since the lesion is not primarily of inflammatory nature and is not composed of syncytiotrophoblast. As the currently preferred name indicates, it is believed to be the result of excessive but otherwise normal infiltration of the implantation site by intermediate trophoblast (Fig. 33.88). Its distinction from placental site trophoblastic tumor can be difficult because the cytologic and immunohistochemical features are very similar. Exaggerated placental site is to be favored when the lesion is microscopic in size, lacks mitotic activity, contains a hyaline material between the trophoblastic cells, and is admixed with decidua and villi.

Placental site nodules and plaques appear as single or multiple, mostly well-circumscribed, variably cellular round or flat lesions (nodules and plaques, respectively) that tend to be extensively hyalinized (Fig. 33.89).[817,818] Most cells have abundant amphophilic or acidophilic cytoplasm, irregularly shaped nuclei, and very scanty mitotic activity, but others have a glycogen-rich clear cytoplasm.[819] Mallory bodies (representing abnormal cytoplasmic aggregates of keratin filaments) may be present.[820] These nodules and plaques, which can also occur in the cervix, fallopian tube, and other sites,[821,822] are distinguished from placental site trophoblastic tumor because of their smaller size, better circumscription, extensive hyalinization, degenerative appearance, and paucity of mitotic activity.[823,824] It has been pointed out that placental site nodules and plaques closely resemble the intermediate trophoblast of the chorion laeve rather than that at the implantation site. As such, they are diffusely positive

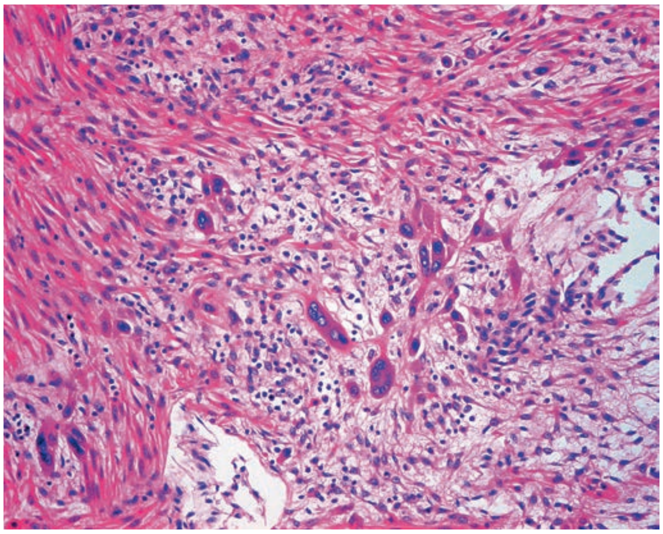


Figure 33.88 Trophoblastic cells infiltrating the myometrium in a tumorlike fashion in exaggerated placental site reaction.

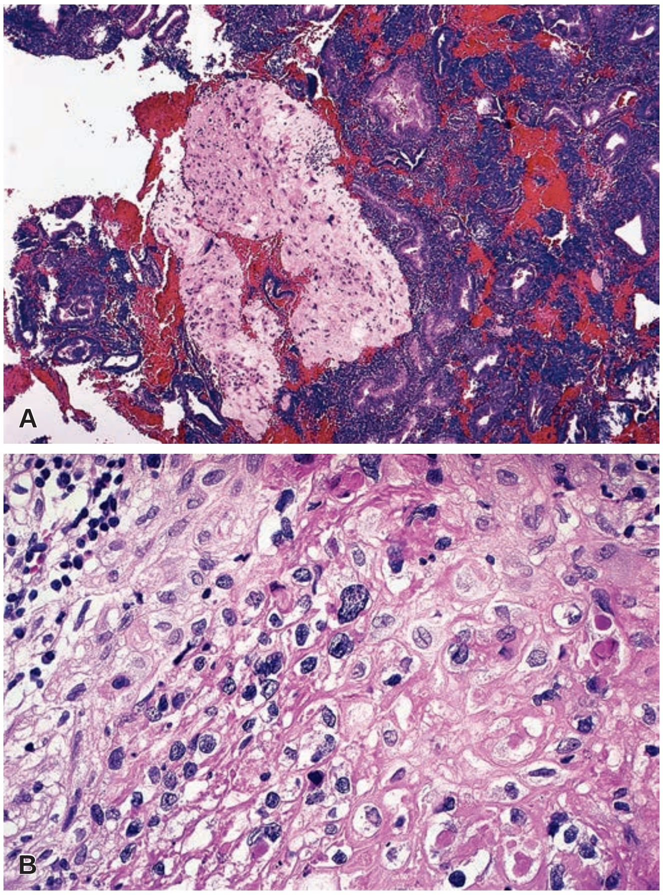


Figure 33.89 **A** and **B,** Low- and medium-power appearance of placental site nodule. The appearance is vaguely chondroid and can be easily misinterpreted.

for PLAP but only focally positive or negative for hPL and CD146 (Mel-CAM).[819]

The differential diagnosis between placental site trophoblastic tumor and the non-neoplastic proliferations previously mentioned may not be always possible in a curettage specimen. In such cases, subsequent curettings and monitoring of serum levels of hCG and hPL become imperative.

Other Tumors and Tumorlike Conditions

Postoperative spindle cell nodules similar to those occurring in the vagina have been observed in the endometrium.[825]

Idiopathic granulomas similar to those more commonly seen in the ovary (and known there as idiopathic ovarian cortical granulomas) have been occasionally seen in the uterus. Most of them were multiple and located in the myometrium.[826]

Extramedullary hematopoiesis can occur in the uterus in the absence of any hematologic disorder or systemic disease (but see Granulocytic [myeloid] sarcoma later).[827] Most of the reported cases have been located in endometrial polyps or leiomyomas and have been associated with chronic anemia.[828]

Myxoid changes can occur in the myometrium in the absence of any other pathology.[829]

Adenomatoid tumors identical to those more commonly seen in the fallopian tube are sometimes found in the uterine wall, usually beneath the serosa and close to the cornua.[830,831] Exceptionally, they will be apparent in a curetting specimen. These tumors are usually small (mean diameter, 2 cm) and macroscopically are usually mistaken for leiomyomas. They are characterized microscopically by adenoid, angiomatoid, solid, and cystic patterns occurring singly or in combination (Fig. 33.90).[832,833] The most cystic examples can simulate lymphangiomas. Their mesothelial nature has been established on the basis of ultrastructural and immunohistochemical findings (including reactivity for calretinin, WT1, and D2-40).[834–839]

Arteriovenous fistula in the wall of the uterus may produce large pulsating masses. The vascular connections are demonstrable by angiography.[840]

Benign mesenchymal tumors other than those already described are extremely rare. They include *hemangioma* of the endometrium,[841] *solitary fibrous tumor* (some associated with hypoglycemia),[842,843] and *lipoma.* The latter may result, at least in some instances, from adipose metaplasia of leiomyomas.[569,570]

Sarcomas of types other than those already described can arise in the uterus. They include *chondrosarcoma,*[846] *osteosarcoma,*[847] *rhabdomyosarcoma,*[848–851] *malignant peripheral nerve sheath tumor,*[852] *angiosarcoma,*[853–855] so-called *malignant fibrous histiocytoma,*[856] *malignant mesenchymoma* (one arising in a leiomyoma),[857] *alveolar soft part sarcoma,*[858] GIST,[859] so-called *rhabdoid sarcoma,*[860] *Ewing sarcoma/PNET,*[861–863] and *tumors with neuroectodermal differentiation* but lacking the *EWSR1* gene rearrangement (Fig. 33.91).[864,865] Some of these sarcomas have developed following radiation therapy for cervical carcinoma or other malignancies.[866] Some of the angiosarcomas have been of epithelioid type, immunoreactive for keratin, and apparently arising within leiomyomas.[867]

Before making a diagnosis of uterine sarcoma (particularly if the tumor is very pleomorphic and/or with heterologous elements), the more likely possibility of an MMMT with predominance of the sarcoma-like component should be ruled out with thorough sampling.[868]

Malignant lymphomas can present initially in the endometrium (including an endometrial polyp[869]), myometrium, or both.[870–873] The patients typically complain of bleeding and a mass. Most tumors are of diffuse large B-cell type.[874–876] Cases of low-grade B-cell lymphoma (including marginal zone B-cell lymphoma),[876,877] T-cell lymphoma,[878] Hodgkin lymphoma,[879] angiotropic lymphoma,[880] and intravascular large B-cell lymphoma[881] with primary uterine involvement have also been described. Malignant lymphomas should be distinguished from florid but reactive lymphoid proliferations involving the endometrium (lymphoma-like lesion),[882,883] and massive lymphoid infiltration of leiomyomas (see earlier). In these benign conditions,

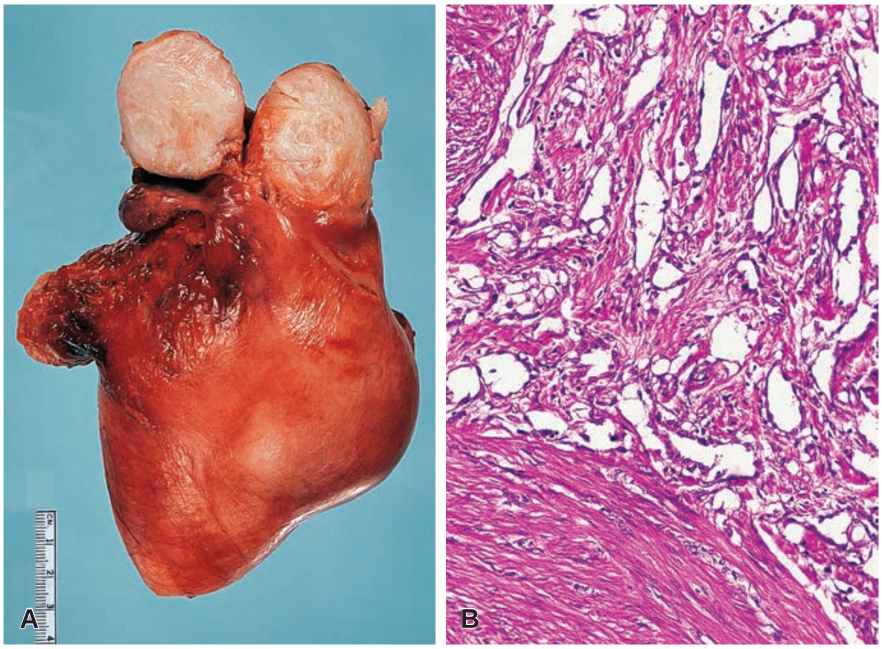


Figure 33.90 **A** and **B,** Adenomatoid tumor of uterus. **A,** Gross appearance. The location at one of the cornua is characteristic. **B,** Microscopic appearance showing tubular formations lined by flattened mesothelial cells.

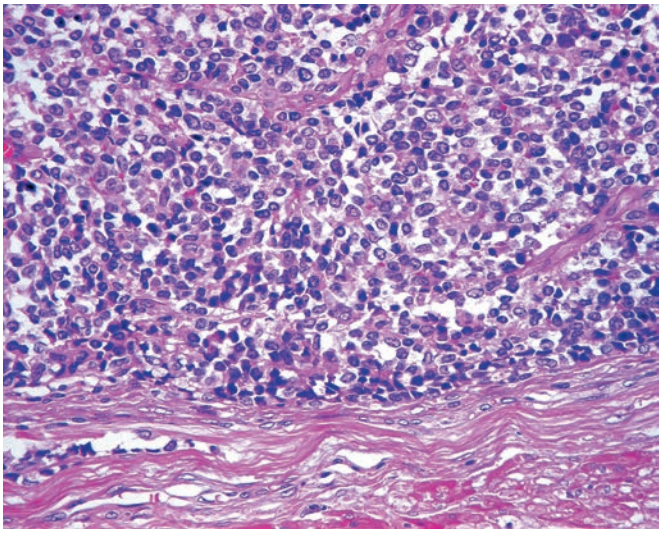


Figure 33.91 Ewing sarcoma/primitive neuroectodermal tumor presenting as a uterine mass, a most unusual occurrence.

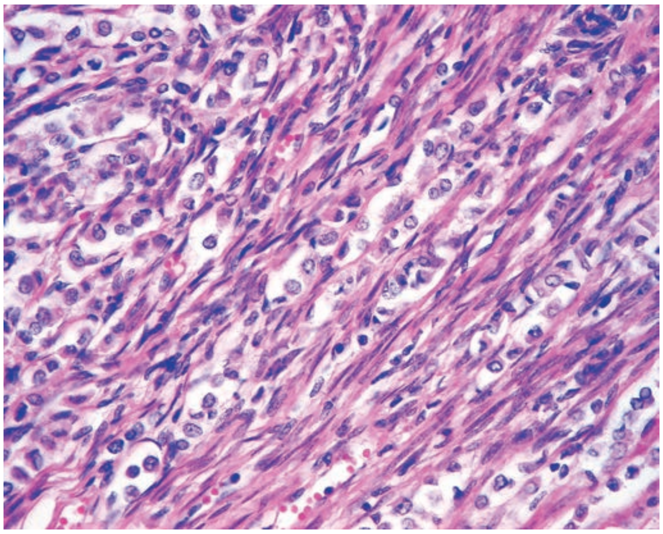


Figure 33.92 Lobular breast carcinoma metastatic to myometrium. Note the Indian file pattern of growth.

the large lymphoid cells are usually accompanied by plasma cells, small lymphocytes, and/or neutrophils.[884] **Granulocytic (myeloid) sarcoma** and **plasmacytoma/myeloma** can also involve the uterus, occasionally as the first manifestation of the disease.[871,885–887]

Other exceptionally rare primary uterine tumors include **Brenner tumor**[888] (microscopically identical to its ovarian counterpart and sometimes having a polypoid configuration),[889] **extrarenal Wilms tumor** (with or without teratoid features),[890,891] **desmoplastic small cell tumor**, **glioma**,[892] **carcinoid tumor**,[893] **paraganglioma**[894] (including a pigmented variant[895]), and **yolk sac (endodermal sinus) tumor**.[896]

Metastatic carcinoma from extrapelvic sites may metastasize to the uterus and cause uterine bleeding as the presenting symptom. The breast, gastrointestinal tract, kidney, and skin (melanoma) are the most frequent primary sites.[897–899] The myometrium is more often involved than the endometrium (Fig. 33.92) and sometimes the leiomyomas present contain metastatic tumor; however, it is not rare for the malignancy to be present in material from endometrial curettings, especially in cases of lobular carcinoma of the breast,[900] and also with neuroendocrine carcinomas and other neoplasms.[901] Exceptionally, a well-differentiated mucinous neoplasm of the appendix will coat the endometrial surface in a pseudomyxomatous fashion.[902] On occasion, a metastatic breast lobular carcinoma has been seen involving a tamoxifen-associated endometrial polyp,[903] and a melanoma has been seen to metastasize into a uterine adenomyoma.[904]

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34

Fallopian Tube

Blake Gilks

CHAPTER CONTENTS

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Normal Anatomy

The **fallopian tube** or salpinx is a tubular hollow structure measuring 11–12 cm in length that runs throughout the apex of the broad ligament and spans the distance between the uterine cornus and the ovary. It is divided into four segments: *intramural* (inside the uterine wall), *isthmus* (2–3 cm, thick-walled), *ampulla* (a thin-walled expanded area), and *infundibulum* (a trumpet-shaped ending that opens into the peritoneal cavity through the ostium and is fringed by the *fimbriae*). One of the latter structures, known as the *ovarian fimbria*, attaches the tube to the ovary.

The inner aspect of the tube is lined by mucosa arranged in the shape of longitudinal, branching folds (known as *plicae*), which merge with the fimbriae. There is good correlation between the microscopic features of this mucosa and its salpingoscopic appearance.[1] Microscopically, the epithelium is composed of three distinct cell types: *secretory*, *ciliated*, and *intercalated (peg)*.[2] Amylase is secreted by the epithelium, and its presence can be demonstrated immunohistochemically.[3] Endocrine cells have been found only exceptionally. A low degree of proliferative activity takes place normally in the tubal epithelium, more so during proliferative/follicular phase of the menstrual cycle, compared to the secretory/luteal phase.[4] At the time of menstruation, as well as a few days postpartum, the tubal mucosa may be normally infiltrated by neutrophils, probably as a reaction to blood and necrotic debris ("*physiologic salpingitis*"); it is accompanied by negative cultures and should not be confused with a bacterial or other infectious salpingitis.[5,6]

The muscular wall *(myosalpinx)* is composed of an inner circular layer and an outer longitudinal layer; the isthmus near the uterotubal junction also possesses an inner longitudinal layer.

The lymphatics of the fallopian tube leave the tubal wall within the mesosalpinx, where they join efferent lymphatics from the ovary and uterus and follow the ovarian vessels to terminate in the aortic lymph nodes. Other lymphatics course within the broad ligament and drain into the interiliac nodes; a separate lymphatic channel from the ampulla of the tube follows the broad ligament to terminate in the superior gluteal lymph nodes.

The **broad ligament** is the peritoneal fold that supports the uterus on either side, extending from this organ to the pelvic wall. It comprises the mesovarium, mesometrium, and mesosalpinx. The broad ligament and the adjacent areas contain a variety of tubular structures related to the müllerian and wolffian systems that may give rise to grossly evident cysts.[7] Most of these are lined by müllerian-type epithelium and have been variously referred to—depending on their specific location and presumed histogenesis—as *parovarian cyst*, *paratubal cyst (hydatid of Morgagni)*, *subserosal müllerian cyst*, *Kobelt cyst (appendix vesiculosa)*, *paroöphoron cyst*, *epoöphoron cyst*, and *rete ovarii cyst*.[8] *Walthard cell nests*, which can also be cystic, are of a different (probably mesothelial) nature.

The **round ligament** is a fibrous cord attached to the superior lateral border of the uterus that passes over the external iliac vessels and the inguinal ligament to leave the abdominal cavity through the deep inguinal ring. From there, it follows the inguinal canal to anchor itself in the labium majus. It serves to orient the uterus by the fact that its insertion is *anterior* to that of the fallopian tube.

Inflammation

Bacterial infection of the fallopian tube is a common disease, and its incidence keeps increasing. It may follow invasive procedures (such

Abstract

The fallopian tube has received increasing attention in this millennium, leading to the recognition that most extra-uterine high-grade serous carcinomas arise in the tube rather than the ovary. With more careful examination of the fallopian tube, increasing numbers of incidental findings are being identified by surgical pathologists; while most are not clinically significant, some do have implications for patient care, and accurate diagnosis is critically important. In addition to neoplastic changes, inflammatory/infectious processes involving the tube are relatively common; although they usually do not lead to surgery, they can do and it is important to for pathologists to be familiar with the spectrum of inflammatory changes in the tube.

Keywords

Fallopian tube;
infection;
inflammation;
carcinoma;
STIC

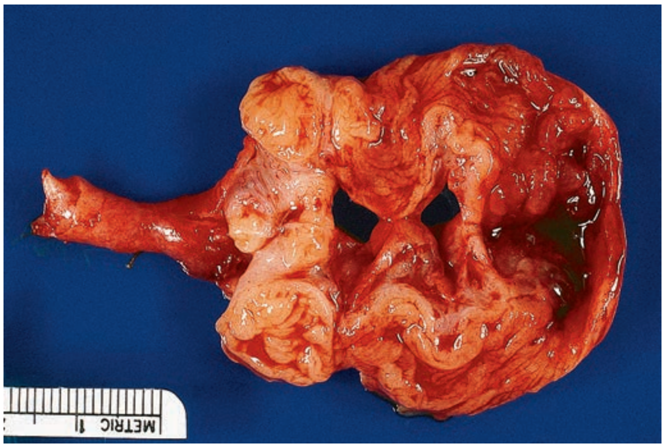

Figure 34.1 Gross appearance of chronic salpingitis with superimposed acute changes.

as curettage or the insertion of intrauterine devices[9]), and it may accompany endometriosis,[10] but in most cases it is due to an ascending infection, often sexually transmitted (Fig. 34.1).[11] The inflammation may result in fusion of tubal plicae and obliteration of the ostium (Fig. 34.2A). Obstruction of the fimbriated end and, less commonly, of the intramural or isthmic portion leads to tubal infertility.[12] Microscopically, the trapped epithelial spaces produce a complicated gland-like pattern that can simulate malignancy (see Fig. 34.2B).[13]

The lumen is often distended and filled with secretions or pus (**pyosalpinx**) (Fig. 34.3). Massive intraluminal hemorrhage may lead to the formation of **hematosalpinx**, a rare condition that needs to be distinguished from the much more common form secondary to ruptured tubal pregnancy. In chronic inflammatory cases, the tubal wall is markedly fibrotic, and serosal adhesions are prominent. The inflammatory exudate often spreads to the ovary, resulting in the formation of a **tubo-ovarian abscess** and obliteration of the pelvic anatomic relationships (Fig. 34.4). The rupture of such an abscess may lead to localized or generalized peritonitis,[14] and it is recommended that fluid collections of greater than 3 cm be drained laparascopically.[15] **Hydrosalpinx** is generally regarded as the end stage of a purulent salpingitis in which pus has been reabsorbed and replaced by a transudate of plasma.[16] The external gross appearance has been likened to that of a retort (Fig. 34.5). Exceptionally, the involvement is limited to the intramural portion of the tube. The wall is thin and fibrotic, with atrophy or even disappearance of the smooth muscle wall. The epithelium is flat and focally absent.

Pelvic inflammatory disease (PID) is the generic term used for inflammatory processes of this region in which the fallopian tube is the epicenter of the inflammation.[17–19] *Neisseria gonorrhoeae* and chlamydia account for most cases.[20–22] Polymicrobial tuboperitoneal infection (resulting from *Bacteroides fragilis*, peptostreptococci, peptococci, and other organisms) is responsible for most of the remaining cases. In established tubo-ovarian abscesses, the most common agents recovered are coliform organisms. *N. gonorrhoeae* was isolated only once in a series of 93 cases by Mickal et al.[14] This finding, however, does not rule out its role as a possible initiating factor before superinfection has occurred, in view of the fact that isolation of *N. gonorrhoeae* is inversely proportional to the number of episodes of salpingitis.[23]

Tuberculosis of the tube develops by the hematogenous route. Most patients are young, and infertility is common.[24,25] In advanced cases, both tubes are replaced by caseous tuberculous masses (Fig. 34.6). There is often extreme proliferation of the tubal mucosa in association with granulomatous inflammation, and this may lead to a mistaken diagnosis of carcinoma. The endometrium is concomitantly involved in approximately 80% of cases.[26]

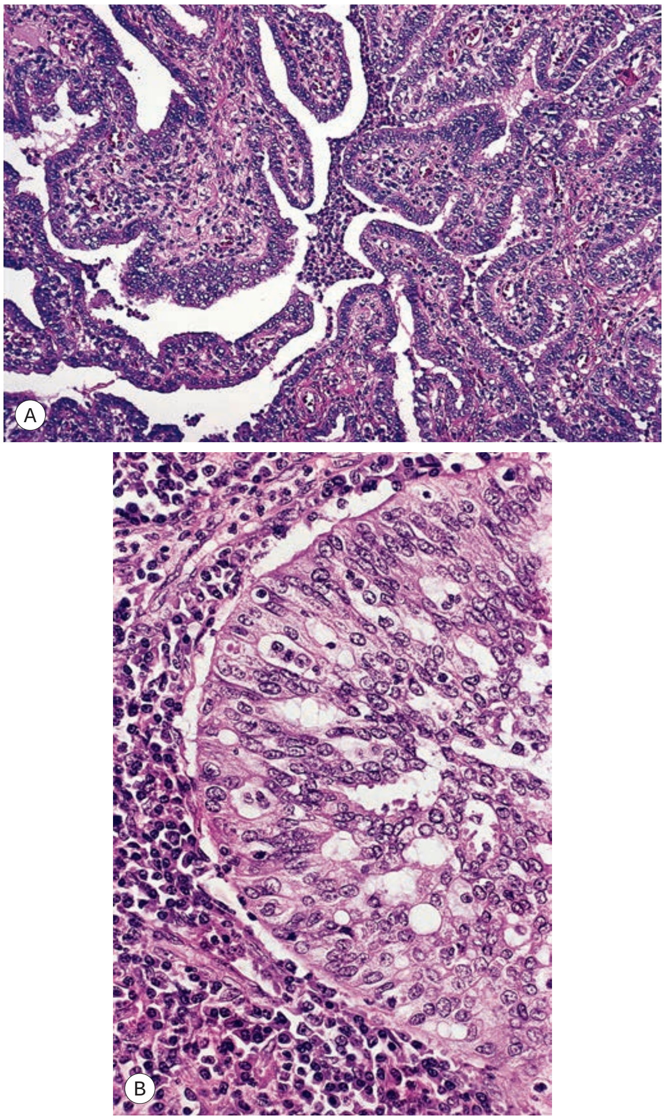

Figure 34.2 **Chronic Salpingitis. A**, Blunting of villi due to heavy inflammatory infiltrate. **B**, Marked secondary reactive hyperplasia of the mucosa, which may simulate a malignant process.

Granulomatous inflammation of the tubes can also be produced by *Schistosoma*, *Oxyuris vermicularis*, *Actinomyces*, *Coccidioides immitis*, and other organisms.[27] *Sarcoidosis* and *Crohn disease* may be accompanied by tubal involvement.

Foreign bodies introduced for diagnostic or therapeutic measures can induce a bizarre granulomatous response (Fig. 34.7). Reaction to the *lipiodol* that used to be introduced in the Rubin test may be so proliferative as to resemble a neoplasm. The push of a uterine sound may drive lubricant into the tube, causing *lipoid granulomas*.[28]

Xanthogranulomatous (pseudoxanthomatous) salpingitis is characterized by an expansion of the tubal plicae by an infiltrate of foamy histiocytes (Fig. 34.8). The distinction some authors make between xanthogranulomatous and pseudoxanthomatous salpingitis is probably unwarranted.[29] Some cases may be due to endometriosis, and, therefore, the term “salpingitis” may be inaccurate.[30] Accordingly, some authors refer to it as *pseudoxanthomatous salpingiosis*.[31]

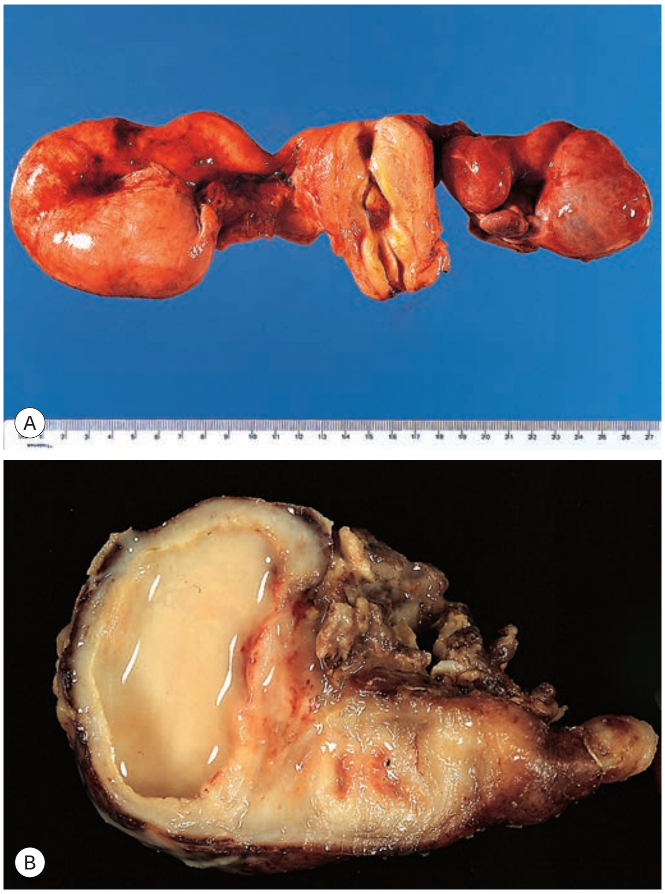

Figure 34.3 **A** and **B**, Outer aspect and cut surface of pyosalpinx. (**A**, Courtesy of Dr RA Cooke, Brisbane, Australia; from Cooke RA, Stewart B. *Colour Atlas of Anatomical Pathology*. Edinburgh: Churchill Livingstone; 2004; **B**, Courtesy of Dr Pedro J Grases Galofrè; from Grases Galofrè PJ. *Patologia ginecològica. Bases para el diagnòstico morfològico*. Barcelona: Masson; 2002).

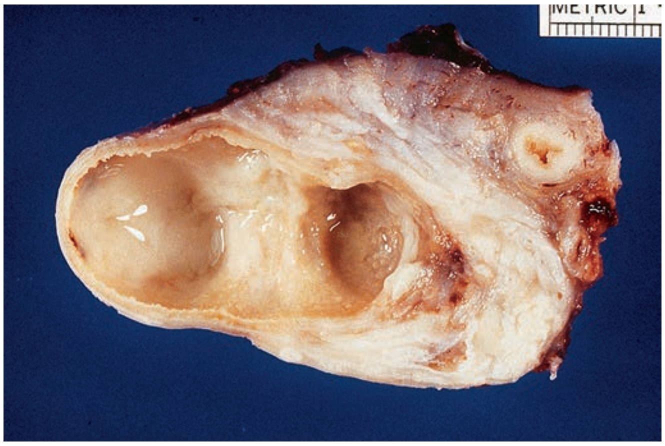

Figure 34.4 Fusion of fallopian tube and ovary into a tubo-ovarian abscess.

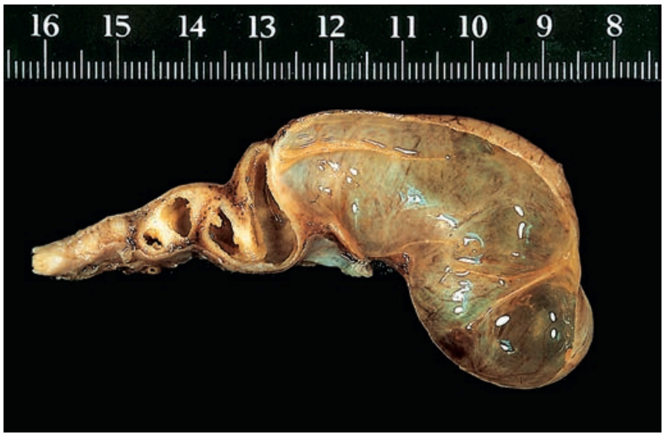

Figure 34.5 Gross appearance of hydrosalpinx showing the typical retort-type appearance. (Courtesy of Dr Pedro J Grases Galofré; from Grases Galofré PJ. *Patología ginecológica. Bases para el diagnóstico morfológico*. Barcelona: Masson; 2002).

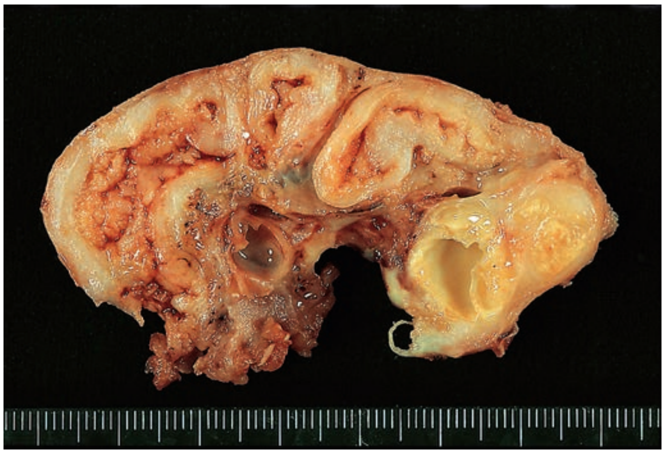

Figure 34.6 Large caseating nodules in tuberculous salpingitis. (Courtesy of Dr Pedro J Grases Galofré; from Grases Galofré PJ. *Patología ginecológica. Bases para el diagnóstico morfológico*. Barcelona: Masson; 2002).

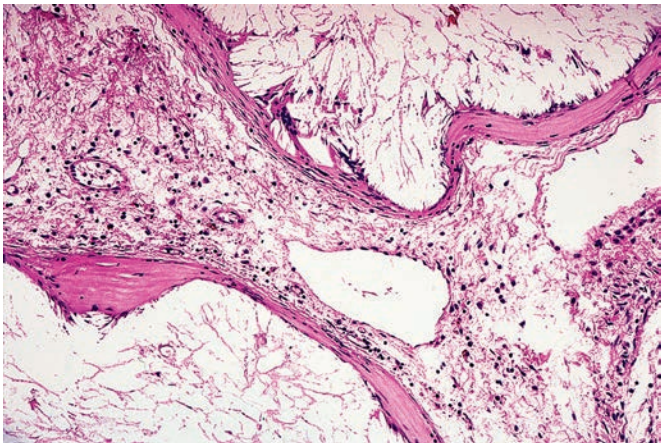

Figure 34.7 Granulomatous reaction to contrast material injected into the fallopian tube.

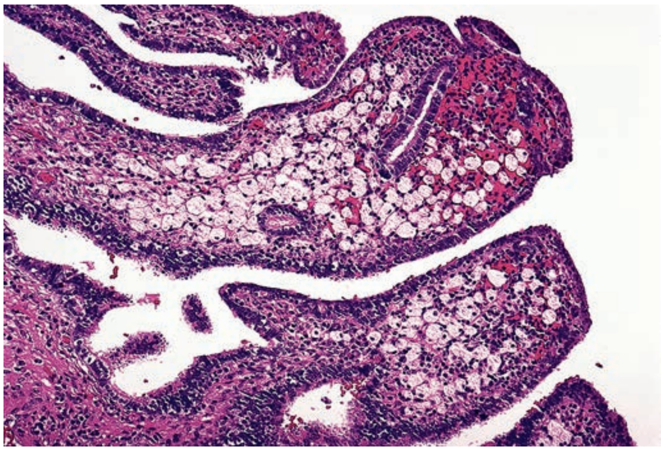

Figure 34.8 Xanthogranulomatous salpingitis.

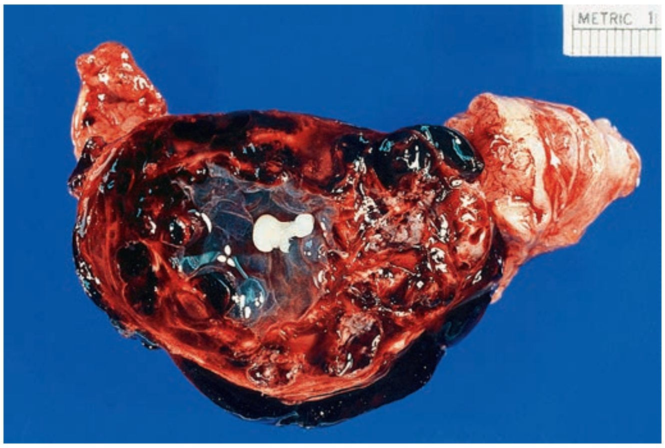

Figure 34.9 Ruptured tubal pregnancy with marked hemorrhage (hematosalpinx). The tiny embryo is identifiable in the center of the clot.

Giant cell arteritis is occasionally found in the tubes, ovaries, and uterus of postmenopausal patients, either as an isolated finding (most frequently) or as a manifestation of a generalized immune-mediated disease.[18,32,33]

Torsion

Torsion of the fallopian tube and ovary is usually secondary to inflammation or tumor, but occasionally it develops in a previously normal organ, the appearance at surgery being that of a hemorrhagic infarct. This phenomenon can occur in adults,[34] as well as in infants and children.[35,36] In children, torsion of the normal adnexa is about one-third as common as torsion of an ovarian cyst or tumor.[37] If the operation (which can be carried out laparoscopically) is done early enough, untwisting of the adnexa may lead to full recovery. Without surgical intervention, cases may resolve spontaneously or result in a necrotic and calcified mass, which may later detach from the uterus. It has been suggested that this complication, when occurring in previously normal adnexa, is due to the fact that the infundibulopelvic ligament extends along the edge of the ovarian ligament so that the tube and ovary hang on a very narrow stalk.

Tubal Pregnancy

The incidence of tubal pregnancy has increased in recent times.[38] It is often the consequence of chronic salpingitis, which leads to inflammatory destruction of the lining folds and retention of the ovum.[39,40] Congenital tubal abnormalities, functional tubal disturbances, and salpingitis isthmica nodosa are responsible for a minority of the cases.[39,41] A history of infertility is associated with an increased risk of tubal pregnancy.[42]

In tubal pregnancy the gestational sac is completely made up of tubal tissue, with no participation from the ovarian or intraligamentary tissues. Following implantation of the ovum in the tubal epithelium (usually in the ampullo-isthmic or midtubal portion), chorionic villi and extravillous (intermediate) trophoblasts can grow predominantly intraluminally[43] or penetrate into the wall, just as they do in the uterus,[39,44] except that the wall here is much thinner. Trophoblastic invasion of muscle and vessels is a common finding of no clinical significance. Hydropic changes and polar trophoblastic proliferation can occur; they should not be overdiagnosed as hydatidiform mole.[45] Changes resembling atherosclerosis may be seen in tubal arteries at the site of implantation, analogous to those occurring in the uterus in orthotopic pregnancy.[46] The fallopian tube epithelium may undergo clear cell hyperplasia.[47] Although a few tubal pregnancies have gone to term,[48] the usual outcome is abortion. The maternal vessels rupture into the gestational sac and cause hematosalpinx (Fig. 34.9). In the presence of a large hematosalpinx, it may be difficult to identify the products of gestation; numerous blocks *from the intratubal blood clot* should be taken for this purpose. Tubal rupture can occur (usually near the end of the second month) because of destruction of the tubal wall by the invading trophoblast, and this may result in severe intra-abdominal hemorrhage. This rupture may result in a brisk reactive proliferation of the mesothelium, with formation of papillae and psammoma bodies. These changes should be recognized as reactive and not misinterpreted as metastases or implants from an ovarian serous neoplasm. The necrotic trophoblastic tissue may be retained for a long time and appear as hyalinized ghost outlines of chorionic villi.[49] On occasion, the appearance of these retained tissues corresponds to that of so-called *placental site nodule*, as described in the uterine corpus.[50,51]

The usual treatment for tubal pregnancy is salpingectomy or laparoscopic salpingostomy (evacuation of the tubal implantation with preservation of the tube).[43,52,53] Conservative laparoscopic procedures for tubal ectopic pregnancy can result in extratubal trophoblastic implants accompanied by persistent beta human chorionic gonadotropin (β-hCG) postoperative serum titers.[54] Exceptionally, omental deposits of fetal parts are seen as a sequela of salpingectomy for ruptured ectopic pregnancy.[55]

Uterine curettings in the presence of a *viable* tubal pregnancy show gestational endometrium, sometimes associated with the Arias-Stella reaction. When trophoblastic elements are not obvious in routinely stained sections from the curettings, some authors have suggested the utility of immunohistochemical stains for hCG, human placental lactogen (hPL), and keratin in the confirmation of an intrauterine pregnancy; however, we have not found this useful in routine practice.[56,57] After death of the embryo or fetus there may be expulsion of the endometrial decidual cast, regeneration of the epithelium, and reestablishment of the cyclic pattern. Therefore, the presence of a proliferative, secretory, or menstrual endometrium in a patient with an adnexal mass does not rule out the possibility of an ectopic pregnancy.

Other Non-Neoplastic Processes

Walthard cell nests are small, glistening, round collections of flat to cuboidal cells with the appearance of urothelium located on the tubal serosa,[58] sometimes accompanied by cystic changes. They are probably of mesothelial rather than müllerian or wolffian nature.[58]

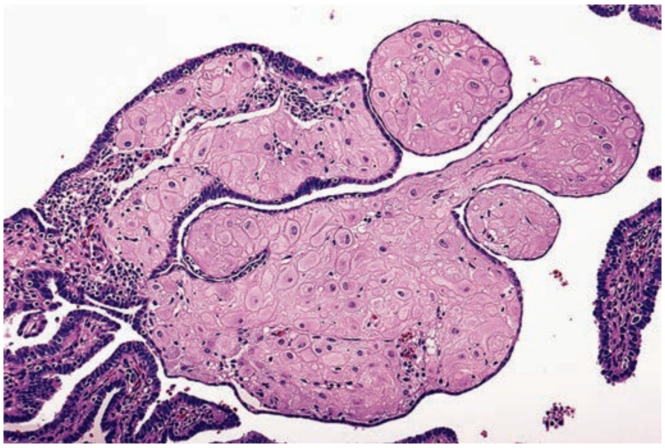

Figure 34.10 Ectopic decidual reaction in the fallopian tube. This is a very common finding during pregnancy.

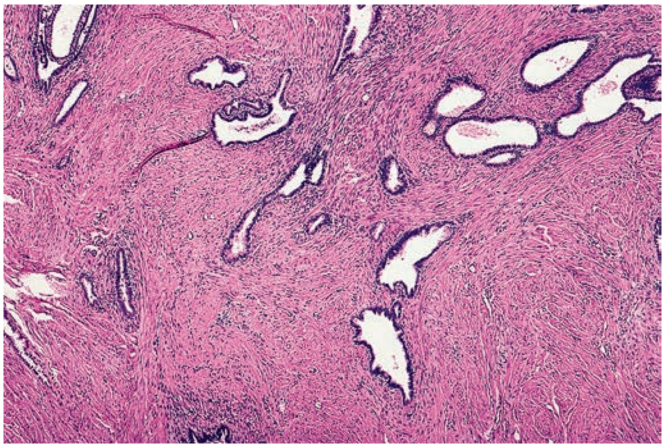

Figure 34.11 Low-power view of salpingitis isthmica nodosa.

They should not be mistaken for serosal implants in patients with ovarian neoplasms.

Paratubal cysts, traditionally known as *hydatids of Morgagni*, are commonly seen as small round cysts attached by a pedicle to the fimbriated end of the tube. Their wall is paper-thin and their content is clear. Occasionally, they attain a large size and may undergo torsion.[59] Most are lined by tubal columnar epithelium containing both ciliated and secretory cells, sometimes projecting in a papillary fashion into the lumen and covered by a thin layer of smooth muscle.[60] Their appearance is consistent with origin from müllerian-type structures. Other paratubal cysts, lined by flat cells and surrounded by a thin fibrous wall, are regarded as of mesothelial origin.[61]

Endometriosis frequently involves the tube in the form of nodules located in the wall or serosa.[62] In this context, it should be mentioned that the most common manifestation of ectopic endometrium in the tube is focal replacement of tubal epithelium by uterine mucosa[63]; however, it is doubtful whether this mucosal colonization of the isthmus by endometrial epithelium and stroma is related to conventional endometriosis; it may, however, be associated with infertility.

Cases have also been reported of the pathogenetically related *müllerianosis* (endometriosis plus endosalpingiosis plus endocervicosis) in the mesosalpinx.[64]

Endosalpingiosis is a term used for the presence of ectopic tubal epithelium beyond the anatomic confines of the tube.[65] It is usually located in the peritoneum but also lymph node and other sites in the pelvis and consists of small cystic structures lined by an epithelium of tubal type cells (secretory, intercalated, and ciliated cells). Since this disorder is often associated with ovarian low-grade serous tumors, it is discussed in more detail in the next chapter.

Decidual reaction of the tubal mucosa is a common finding in specimens of tubal ligation obtained at the time of cesarean section; it appears as small nodular collections of decidual cells covered by a flattened, sometimes inflamed epithelium (Fig. 34.10). Similar changes have been documented following hormonal therapy.[66]

Arias-Stella reaction can occur in the fallopian tube epithelium in association with either orthotopic or tubal pregnancy.[67]

Salpingitis isthmica nodosa is a usually bilateral lesion that presents grossly as a well-delimited nodular enlargement of the isthmic portion of the tube.[65] Microscopically, cystically dilated gland-like formations are seen surrounded by hypertrophic muscle (Fig. 34.11). Radiographic and tridimensional reconstructive studies have shown that the cystic formations are connected to the lumen of the tube. Although classically regarded as the result of inflammation (hence its name), convincing evidence has been presented that its pathogenesis is analogous to that of uterine adenomyosis.[68] It is accompanied by infertility in approximately half of patients, and it may also lead to ectopic pregnancy.[69]

Tubal sterilization procedures can lead to a sequence of morphologic alterations, which include proximal luminal dilation, plical attenuation, chronic inflammation with pseudopolyp formation, and plical thickening in the distal segment.[70] The appearance varies depending on the length of time that has elapsed from the sterilization procedure.[71]

Metaplastic changes of several types can develop in the fallopian tube mucosa. *Transitional cell (urothelial) metaplasia* is usually located in the fimbriae, where it may mimic serous tubal intraepithelial carcinoma (STIC). It is distinguished from it because of the uniformity in cell size and shape, low nucleocytoplasmic ratio, lack of nuclear atypia, presence of nuclear grooves, lack of mitoses, and absence of abnormal p53 expression or increased staining for Ki-67.[72,73] *Eosinophilic metaplasia* (sometimes accompanied by mucinous changes) presenting as a sharply outlined papillary lesion is occasionally encountered; the initial descriptions were in tubes removed in the immediate postpartum period (Fig. 34.12).[74,75] Their behavior is benign. This lesion, which has been called *metaplastic papillary tumor*, is morphologically similar to "papillary tubal hyperplasia," discussed in more detail later. It is an interesting lesion but is not of clinical significance, in that no further treatment is indicated. *Mucinous changes*, probably of metaplastic nature, have also been described in fallopian tubes.[76] When associated with appendiceal and ovarian mucinous tumors, however, we suspect that this is secondary spread to the fallopian tube mucosa, having encountered a case with HER2 amplification in both the primary tumor and fallopian tube mucinous epithelium. It has been described in a patient with Peutz-Jeghers syndrome who had both ovarian mucinous neoplasms and mucinous epithelium in tube and endometrium.[77]

Papillary endothelial hyperplasia can develop in tubal vessels and simulate an angiosarcoma; as in other sites, it is the expression of organization and recanalization of thrombi.[78]

Fallopian tube prolapse into the vaginal apex following vaginal hysterectomy can simulate the microscopic appearance of recurrent endometrial adenocarcinoma or, if the stroma predominates, an aggressive angiomyxoma.[79]

Proliferative Epithelial Lesions

Proliferative epithelial lesions may be found during the microscopic examination of a specimen from tubal ligation or salpingectomy.

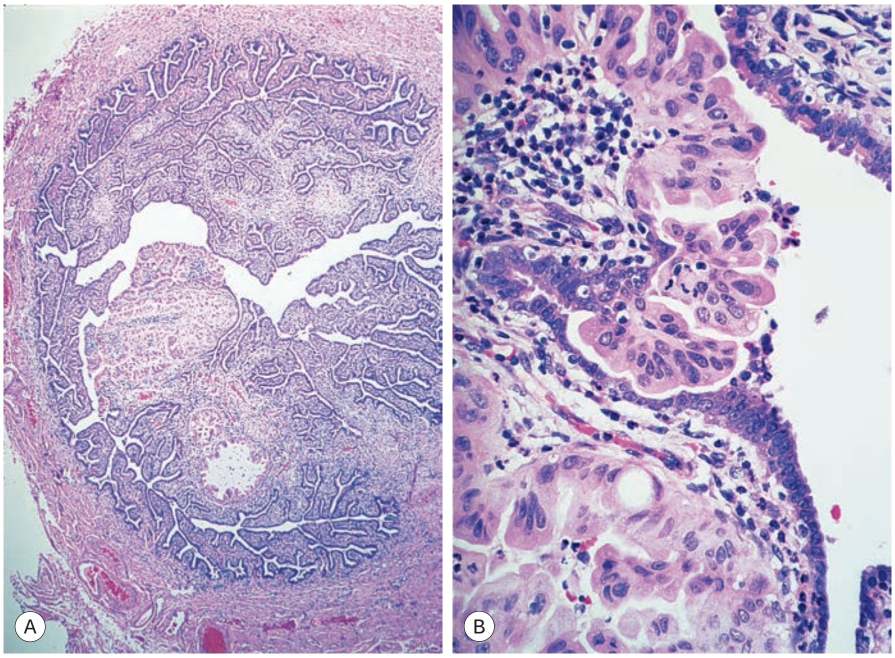

Figure 34.12 **A** and **B**, So-called metaplastic papillary tumor of fallopian tube. This lesion is characterized by a papillary proliferation of acidophilic epithelium. This process is probably the same as "papillary tubal hyperplasia."

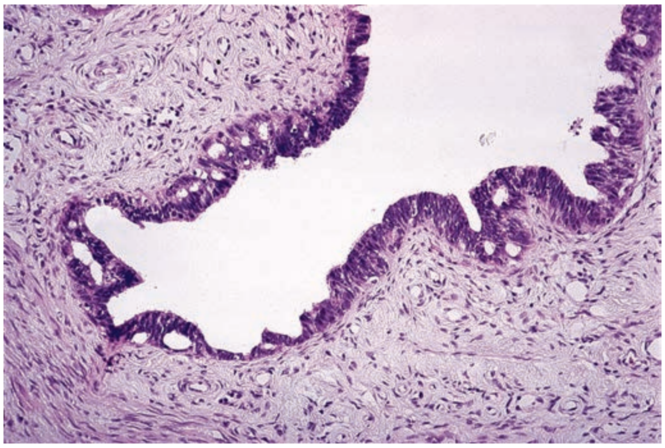

Figure 34.13 Hyperplasia of the tubal epithelium; this is a common incidental finding of no clinical significance and must be distinguished from STIC.

They may show one or more of the following features: nuclear crowding, stratification, loss of polarity, mild to at most moderate atypia, occasional mitoses, acidophilic metaplasia, and papillary formations (Fig. 34.13).[80] Mild degrees of this change are extremely common; in one study, they were found in 83% of all tubes examined and are benign.[81]

Some of the above changes have been found in association with other lesions or situations, such as salpingitis and exogenous or endogenous estrogen stimulation; such florid reactive proliferations have in the past been confused with STIC, but lack the high-grade nuclear atypia of STIC and are completely benign.[81–85]

The term **papillary tubal hyperplasia** has been proposed for a papillary lesion composed of rounded papillary clusters of bland tubal epithelial cells that project into the tubal lumen. They can be seen as an incidental finding in salpingectomy specimens from women with serous borderline tumors, or unassociated with any ovarian pathology, and Kurman et al. have suggested that they are precursors of serous borderline tumor and endosalpingiosis.[86] Such a relationship is highly speculative, as they are not seen in association with most serous borderline tumors. In one case *RAS* mutations were found in an ovarian serous borderline and in papillary tubal hyperplasia present in both fallopian tubes, suggesting a clonal relationship.[87] Morphologically, papillary tubal hyperplasia appears to be the same as the metaplastic papillary tumor, described originally by Scully and colleagues as a rare incidental and benign finding in the fallopian tube. It is likely that papillary tubal hyperplasia is more commonly encountered now that fallopian tubes are being more carefully examined, but they remain distinctly uncommon and their relationship, if any, low-grade serous neoplasia remains to be elucidated.

Carcinoma

Traditionally, primary carcinoma of the fallopian tube has been regarded as very rare, accounting for approximately 1% of primary genital tract malignancies.[88] This figure, however, was based on diagnostic criteria that reserved the diagnosis of primary fallopian tube carcinoma for cases where there was minimal ovarian involvement; the presence of ovarian mass(es) resulted in tumors being designated as primary ovarian carcinoma.[89] These criteria are based on the so-called dominant mass theory, which has been thoroughly discredited. For example, ovarian involvement associated with mucinous appendiceal neoplasms, gastric carcinoma, colorectal carcinoma, and cervical adenocarcinoma is frequently larger that the primary tumor, and while the associated ovarian tumors were mistakenly considered to be independent primary tumors in the past, they have been convincingly demonstrated to be metastasis. A superior approach to identification of primary site is to characterize the anatomic site of unifocal lesions of high-grade serous carcinoma (HGSC), before there is metastatic spread and involvement of multiple sites. In both sporadic and hereditary cases of HGSC the earliest,

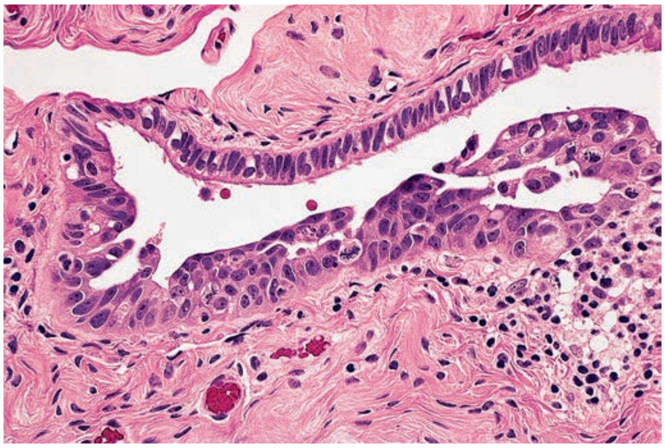

Figure 34.14 **Serous Tubal Intraepithelial Carcinoma.** Note the abrupt transition from benign tubal epithelium to cells with pleomorphic nuclei. Abnormal p53 immunostaining and a high (>10%) Ki-67 labeling index can help confirm the diagnosis.

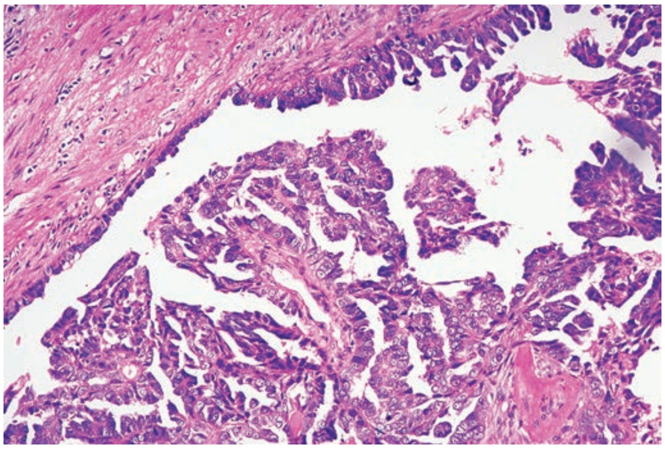

Figure 34.15 High-power view showing the complex papillary architecture that is characteristic of high-grade serous carcinoma.

unifocal lesions are almost always in the fallopian tube.[89,90] There are certainly cases of HGSC where the fallopian tube is normal, even after careful examination, but these are a minority.[90]

Serous Tubal Intraepithelial Carcinoma

The earliest fully malignant lesion of HGSC is STIC. It most commonly, but not exclusively, involves the fimbriae and is characterized by increased nucleus to cytoplasm ratio with rounded nuclei, loss of cell polarity, coarsely clumped chromatin, prominent nucleoli, and the presence of mitotic activity involving non-ciliated (i.e., secretory) cells (Fig. 34.14). The cells are morphologically identical to those seen in HGSC, and the immunophenotype is also the same with WT1 expression, high (usually >50%) Ki-67 labeling index, and abnormal p53 staining. The diagnostic criteria for STIC have since evolved and guidelines for diagnosis have been published, which include the use of p53 and Ki-67 immunostaining[91–93]; high-grade nuclear atypia, together with abnormal p53 staining and a Ki-67 labeling index greater than 10% allow for a reproducible diagnosis of STIC.[93] Adherence to these criteria results in a high degree of interobserver diagnostic agreement. In practice, immunohistochemistry can be reserved for those cases where morphology alone is insufficient for unequivocal diagnosis; a diagnosis of STIC in a patient with advanced stage HGSC can usually be made without resorting to immunostains.

Fallopian tube epithelial lesions with atypia that do not meet all the criteria for STIC are variously referred to as tubal intraepithelial lesion in transition (TILT) or serous tubal intraepithelial lesion (STIL).[94–97] These lesions are of uncertain significance and, in our opinion, these diagnostic terms should not be used in routine practice; additional research is required to determine the clinical significance, if any, of such lesions. Similarly p53 signatures should not be reported. These take the form of small foci of intense p53 nuclear staining involving consecutive secretory cells, most commonly but not exclusively in the fimbriae, in the absence of cytologic atypia.[98] p53 signatures are common in normal fallopian tube and should not be commented on in a diagnostic surgical pathology report.

STIC, if unassociated with invasion or extratubal disease, will usually follow a benign course.[99,100] Exceptions have been reported. As is the case with serous carcinoma of endometrium confined to a polyp, the favorable prognosis of STIC is only true if there has been an adequate staging procedure, as apparently noninvasive STICs have been associated with trans-coelomic spread and stage III disease. Thus, only when there has been confirmation of no extratubal disease should observation be elected in patients with incidentally diagnosed STIC.

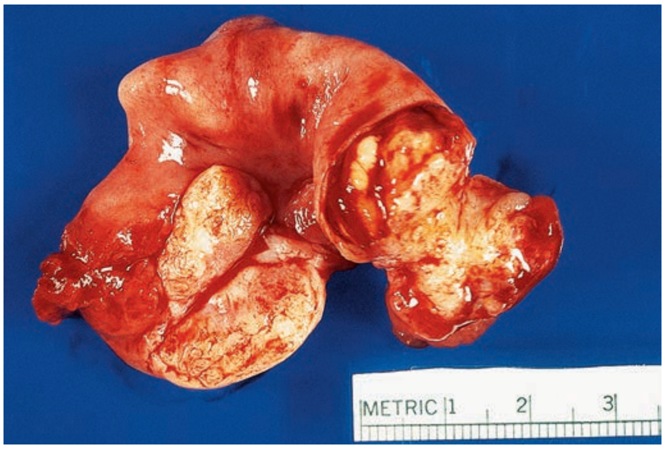

Figure 34.16 Fallopian tube filled by high-grade serous carcinoma. This uncommon finding is seen in association with obstruction of the fimbrial end of the tube.

High-Grade Serous Carcinoma

The clinical and pathologic features of HGSC are the same, whether the tumor is considered to have arisen in fallopian tube, ovary, or peritoneum (Fig. 34.15). There has been a shift in our understanding of where most HGSC originate,[89] but it has not impacted significantly on management our outcomes. In keeping with tradition, we will leave a more comprehensive discussion of HGSC for the section on ovarian carcinoma, later in this chapter, even though there is evidence that most arise in the fallopian tube.[89,90] Although most patients with HGSC present with ascites and an adnexal mass, the nature of the adnexal involvement can vary. In patients with predominantly tubal involvement, a history and/or morphologic evidence of coexisting or preceding salpingitis is common, and reduced access by tumor cells to the peritoneal cavity may explain the unusual tumor distribution (Fig. 34.16). Staging of HGSC is the same, whether the tumor is considered to have arisen from fallopian tube and ovary.

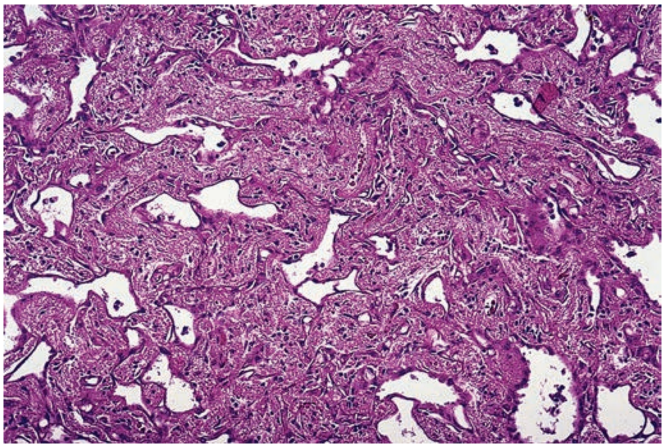

Figure 34.17 Adenomatoid tumor of fallopian tube accompanied by smooth muscle hyperplasia.

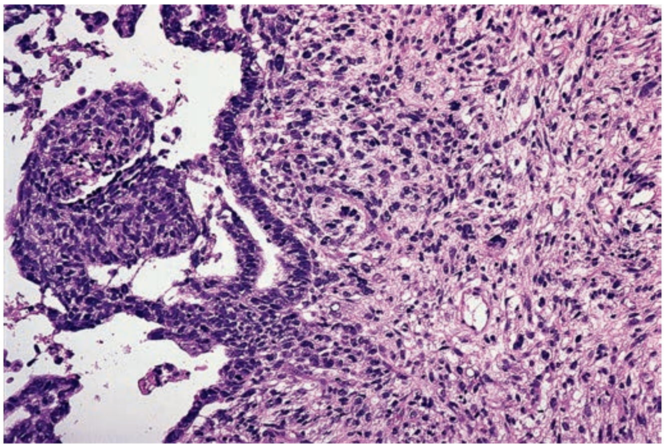

Figure 34.18 Carcinosarcoma (malignant mixed müllerian tumor) of fallopian tube, showing the typical biphasic pattern.

Other Carcinomas

Although HGSC is most common, all carcinomas reported in the ovary can occur in the fallopian tube, including endometrioid (the second most common type, including spindle cell, oxyphilic, adenoacanthomatous, adenosquamous, and squamous types), mucinous, seromucinous, clear cell, and hepatoid.[11,101–107] The endometrioid carcinomas typically present as intraluminal masses and may microscopically simulate a neoplasm of wolffian origin.[108]

A carcinoma extensively involving both endometrium and tube should be classified as a primary endometrial tumor; serous carcinoma of the endometrium involves the fallopian tube in 20% of cases when the fallopian tube is carefully examined.[109] Such tumors stain as would be expected of endometrial serous carcinoma, with weak or negative WT1 staining, in contrast to the strong WT1 positivity characteristic of tubo-ovarian HGSC.

Borderline epithelial neoplasms have also been described in the fallopian tube. As in the ovary, they can be of serous, endometrioid, or mucinous type.[110,111]

Other Tumors

Adenomatoid tumor is a benign, usually small lesion that may be found within the wall of the tube or beneath the uterine serosa near a cornu.[112] The gross and microscopic features are identical to those of its epididymal counterpart (see Chapter 27). The ill-defined, seemingly infiltrating margins may lead to a mistaken diagnosis of carcinoma.[113] A marked degree of smooth muscle hyperplasia may be present and obscure the true nature of the lesion (Fig. 34.17). There is now agreement on the basis of ultrastructural and immunohistochemical findings (the latter including positivity for calretinin, WT1, CK5/6, and D2-40[112,114]) that this entity is of mesothelial (rather than wolffian, müllerian, or endothelial) derivation and that it represents a unique variant of benign mesothelioma largely restricted to the genital region,[115,116] as originally postulated by Pierre Masson.

Papillary cystadenoma of the mesosalpinx has been seen in patients with von Hippel–Lindau disease.[88] Allelic deletions of the *VHL* gene have been detected in these cases.[117]

Mucinous lesions of the fallopian tubes comprise a wide variety of processes, which include mucinous metaplasia (see earlier), mucinous cystadenoma, "mucinous borderline tumor," and mucinous adenocarcinoma. Some of these lesions have occurred in patients with Peutz-Jeghers syndrome, others in association with in situ or invasive adenocarcinoma of other portions of the female genital tract (such as endocervix), and still others in conjunction with mucinous neoplasms of the appendix.[118,119] It is likely that the latter are tubal metastases or implants of appendiceal primaries.

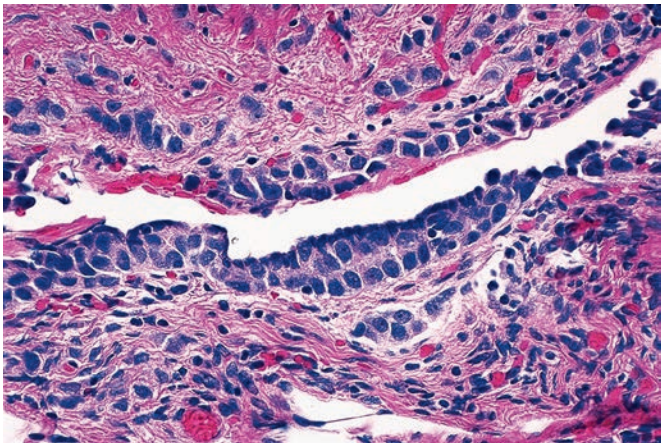

Figure 34.19 Metastatic lobular carcinoma of breast growing beneath tubal epithelium.

Approximately 50 cases of tubal **teratomas** have been published, nearly all cystic and benign[120]; one of them contained a *carcinoid tumor* and another was entirely composed of mature thyroid tissue *(struma salpingis)*.[121] Other reported benign tubal tumors, all very rare, are **leiomyoma, hemangioma, adenofibroma,**[122–124] **sex-cord tumor with annular tubules** (associated with endometriosis),[125] and **papilloma**.[121] The latter should be distinguished from the more common papillary hyperplasia associated with inflammation and hyperestrinism.

Malignant tumors other than carcinoma include **carcinosarcoma (malignant mixed müllerian tumor)**[88,124,126–128] (some bilateral[129]) (Fig. 34.18), **leiomyosarcoma**, **gestational choriocarcinoma**,[130] and **synovial sarcoma**.[131] The first three tumor types resemble, grossly and microscopically, their more common uterine counterparts; tubal extension from the latter should always be considered in the differential diagnosis. Tubal involvement by **malignant lymphoma** is always the expression of systemic disease. Most **metastases** to the tube originate from other genital organs (Fig. 34.19).[111]

Tumors and Tumorlike Conditions of Broad and Round Ligaments

The **round and broad ligaments** are only rarely the site of primary disease.[107,132] **Striated muscle heteroplasia** is an inconsequential incidental finding, thought to represent aberrant persistence of gubernacular rhabdomyoblasts.[133]

Cystic formations derived from müllerian or mesonephric (wolffian) rests can be found in or around the broad ligament.

Wolffian tumor (female adnexal tumor of probable wolffian origin) is a distinctive lesion originally described in the broad ligament and subsequently also recognized in the ovary. In its most typical form, it is seen within the leaves of the broad ligament or hanging on a pedicle from it or the fallopian tube. Grossly, it is predominantly solid. Microscopically, it is composed of epithelial cells growing in diffuse, trabecular, and tubular patterns (Fig. 34.20). Mitotic activity and capsular invasion may be present, but the prognosis is generally good.[134,135] The differential diagnosis of wolffian tumor includes endometrioid carcinoma and sex cord–stromal tumor. The presence in the broad ligament is a finding in favor of wolffian tumor. Caution must be used in interpretation of immunostains as there is often expression of sex cord–stromal markers, and inconsistent expression of markers of mesonephric differentiation, such as GATA3.

Other tumors and tumorlike conditions that can be found in the broad ligament unassociated with either uterine or ovarian disease are *endometriosis* (including the possibly related condition known as uterus-like mass)[136]; *borderline serous tumors*[137]; *serous*, *endometrioid*, *clear cell*, and *mucinous carcinomas*[138,139]; *papillary cystadenomas* and other neoplasms associated with von Hippel–Lindau disease[140,141]; *ependymoma*[142]; *smooth muscle tumors*; and other types of *mesenchymal neoplasm*. Some of the carcinomas of this region are thought to arise from foci of endometriosis.[139]

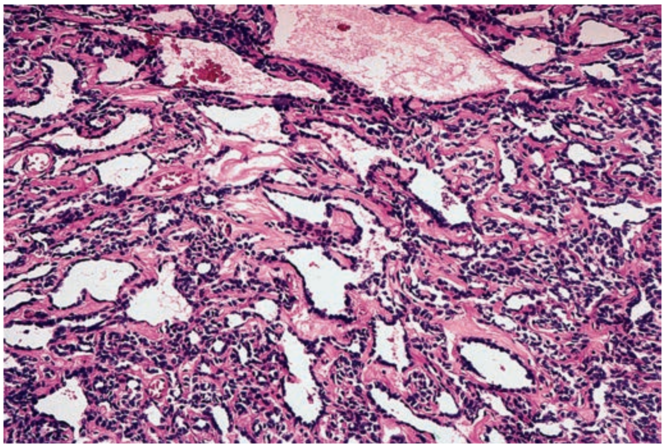

Figure 34.20 Wolffian tumor of the broad ligament. The sieve-like low-power appearance is characteristic.

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Ovary

35

Blake Gilks

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Normal Anatomy

The ovaries are paired pelvic organs located on the sides of the uterus close to the lateral pelvic wall, behind the broad ligament and anterior to the rectum. They are connected to the broad ligament by the mesovarium (a double fold of peritoneum), to the uterine cornu by the ovarian (or utero-ovarian) ligament, and to the lateral pelvic wall by the infundibulopelvic (or suspensory) ligament. During the reproductive period, their average size is 4 × 2 × 1 cm and their average weight is 5–8 g; after menopause, they shrink to one half or less of this size.

The ovarian lymph vessels drain to large trunks that form a plexus at the hilus, from which they travel through the mesovarium to drain into the para-aortic nodes; others drain into the internal iliac, external iliac, interaortic, common iliac, and inguinal nodes.

The ovary is covered by a single layer of modified mesothelium known as *ovarian surface epithelium* or OSE. This epithelium is immunoreactive for keratin, epithelial membrane antigen (EMA), Ber-EP4, CA 125, vimentin, estrogen and progesterone receptors (ER and PR), and follicle-stimulating hormone.[1,2] Epithelial inclusion glands/cysts are commonly found in the cortex. Interestingly, although the OSE is negative for PAX8, the lining cells of the epithelial inclusion cysts are typically PAX8 positive.[3]

The *ovarian stroma* is divided into a cortical and a medullary region, but the boundaries between them are indistinct. It is composed mainly of spindle-shaped stromal cells resembling fibroblasts, typically arranged in whorls or a storiform pattern. The cells may contain cytoplasmic lipid and are surrounded by a dense network of reticulin fibers. They are immunoreactive for FOXL2, ER, and PR.[1] Some of these cells have myoid ("myofibroblastic") features and exhibit immunoreactivity for smooth muscle actin and desmin.[4,5] Foci of smooth muscle hyperplasia may be found, most often in perimenopausal or postmenopausal women.[4] Metaplastic bone formation can also occur.[6] Other cells that may be found in the ovarian stroma are luteinized stromal cells (singly or in small nests, mainly in the medulla), decidual cells, nests of cells resembling endometrial stromal cells, mature fat cells, and neuroendocrine cells.[1,6,7]

The life cycle of the *ovarian follicle* includes primordial, maturing (primary, secondary, tertiary, and graafian), and atretic forms, together with corpora lutea and corpora albicantia for those that have reached full maturation. Primordial follicles contain germ cells that have originated from the yolk sac endoderm and migrated into the ovary, where they develop into oogonia and oocytes.[1] The maturing follicle is composed of the oocyte, the granulosa layer, and the two theca layers. *Granulosa cells* lack a reticulum around them and are immunoreactive for vimentin, FOXL2, and ER and show variable/weak immunoreactivity for keratin.[1] They feature small rosettelike formations known as Call–Exner bodies, which contain at their center a deeply eosinophilic filamentous material consisting of excess basal lamina. The stroma-derived *theca cells* form an internal layer (which is typically luteinized) and an external layer (which is very cellular and can simulate a neoplastic process

Abstract

A broad range of pathologic conditions are encountered in the ovary in routine surgical pathology practice. Indeed, there is no organ in the body that can lay claim to a greater variety of primary neoplasms. This reflects the complex function of the ovary in reproduction, as site of germ cells and their supporting sex cord–stromal cells; both cell types can give rise to benign or malignant tumors. The most common ovarian neoplasms, however, are epithelial. Although the histogenesis of epithelial ovarian tumors of different cell types (histotypes) remains controversial, recent years have seen significant advances and these have solidified the important concept that the different histotypes of epithelial ovarian cancer are distinct diseases. This, in turn, has led to an emphasis on accurate histotype diagnosis by surgical pathologists.

Keywords

Ovary,
neoplasia,
borderline,
carcinoma,
sex cord–stromal,
germ cell.

when cut tangentially). Internal theca cells are an important site of sex steroid production, as determined indirectly by the immunohistochemical detection of enzymes involved in steroid hormone biosynthesis.[8,9]

The mature *corpus luteum* is a 1.5–2.5-cm round yellow structure with lobulated outlines and a cystic center. Both the granulosa and the theca cells that form it show prominent luteinization. Morphologic criteria for the dating of the corpus luteum have been established.[10] The corpus luteum of pregnancy is characterized by its larger size, bright yellow color, prominent central cavity, and the presence of hyaline droplets and calcification.[1]

At the ovarian hilus, there are clusters of cells analogous to testicular Leydig cells known as *ovarian hilus cells*. They are closely associated with large hilar veins and lymph vessels and may form nodular protrusions within their lumina. They also exhibit an intimate relationship with the nerves of the region.[1,11] They may contain Reinke crystalloids, lipids, and lipochrome pigment. Hyperplasia of these cells is found following the administration of chorionic gonadotropin, in pregnancy, and in the presence of choriocarcinoma.[1]

The *rete ovarii*, present in the ovarian hilus, represents the ovarian counterpart of the rete testis. It consists of a network of clefts, tubules, cysts, and papillae lined by an epithelium of variable height and surrounded by a cuff of spindle cell stroma. This epithelium is immunoreactive for keratin and CA 125.[12]

Walthard cell nests may be cystic or solid. They are located in the mesovarium, in the adjacent mesosalpinx, or within the ovarian hilus and have a lining of transitional/urothelial appearance (sometimes mucin producing), which is probably of mesothelial nature.

The previous description mainly pertains to the fully developed ovary in women of childbearing age. The many modifications exhibited by the prepubertal and postmenopausal ovary are beyond the scope of this chapter. It should be mentioned, however, that prominent cystic follicles are normally seen during the first few months of life and at puberty and that the shrunken postmenopausal ovary ("ovarium gyratum") has thick-walled medullary and hilar vessels (which should not be mistaken for hemangiomas). These atrophic ovaries may also contain clinically inconsequential granulomas and hyaline scars.[1]

The immunohistochemical profiles of the various cell components of the ovary are discussed further in connection with the tumors of the respective structures.

Gonadal Dysgenesis

Patients with gonadal dysgenesis have abnormally developed gonads and infantile sexual development. The conditions mentioned here are mainly those associated with an abnormal sex chromosome constitution ("abnormalities in sex determination"), to be distinguished from those such as male and female pseudohermaphroditism, persistent müllerian duct syndrome (due to a defect in the müllerian inhibiting substance system), and end-organ defects[13] ("abnormalities in genital differentiation").[14,15]

Sometimes, gonadal tissue is biopsied or removed in the course of evaluation of these malformations.[16,17]

Klinefelter syndrome is usually characterized by the karyotype 47,XXY and is further discussed in Chapter 27.

In patients with **gonadal dysgenesis**, either "**pure**" (with a 46,XX or 46,XY karyotype) or associated with the somatic features of **Turner syndrome** (with a 45,XO karyotype), both gonads are represented by a streak of fibrous tissue that resembles ovarian stroma (Fig. 35.1).[18–20] These patients do not seem to have an increased incidence of gonadal tumors (in the absence of Y chromosome specific sequences),[21] but various types of nongonadal neoplasm (such as atypical polypoid adenomyoma of uterus, leukemia, and soft tissue tumors) have been reported in patients with the syndrome.[22,23] Also, several cases of Turner syndrome have been reported in association with endometrial adenocarcinoma; in some of these, prolonged estrogen therapy had been administered.[24]

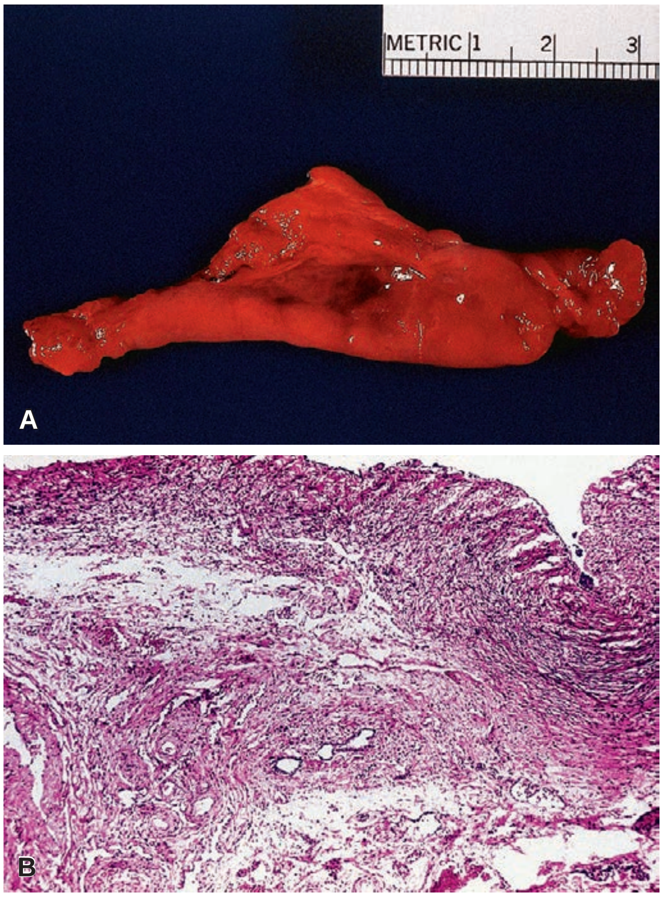

Figure 35.1 **Streak Gonad in Turner Syndrome. A**, Gross appearance; **B**, microscopic appearance.

In **mixed gonadal dysgenesis** (usually characterized by a 45,X/46,XY mosaicism or 46,XY phenotype), one gonad is represented by a streak gonad or streak testis and a contralateral testis (that is typically cryptorchid) or bilateral streak testis.[25] Individuals with this condition are particularly prone to the development of gonadoblastomas, a complication prevented by early removal of the gonads.[26] The tumors may totally obliterate the testicular elements and thus lead to an incorrect typing of the dysgenesis.

True hermaphrodites may have ovotestes containing both ova and immature seminiferous tubules or other combinations of ovary and testis (Fig. 35.2). [27–29] The most common karyotypes are 46,XX (60%), 46,XY (12%), and mosaic (28%). Multiple tumors can occur in these gonads.[30]

The familial syndrome of **testicular feminization** is the most common type of male pseudohermaphroditism. It occurs in individuals with a normal male chromosome constitution with an end-organ defect (androgen insensibility). It is characterized by the presence of several well-developed female secondary sex characteristics. These patients consult a gynecologist because of amenorrhea or sterility. They are found to have a vagina, no uterus, and bilateral cryptorchid testes. The latter often contain nodular masses of immature tubules that should not be confused with Sertoli–Leydig cell tumor (Fig. 35.3).[31,32] The syndrome is of further clinical importance because

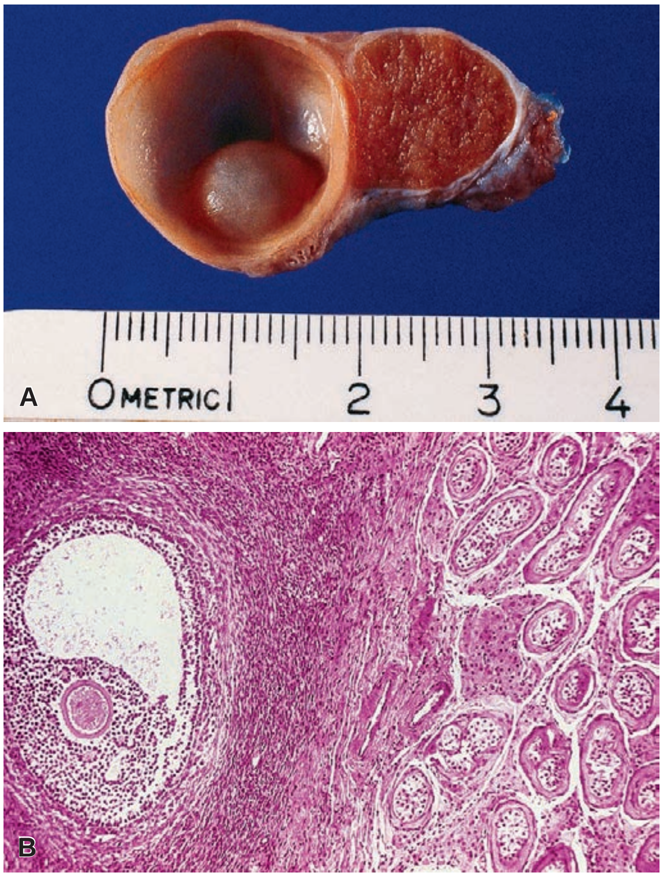

Figure 35.2 Ovotestis in True Hermaphroditism. A, Gross appearance. The testicular component is represented by the solid nodule, whereas the ovarian component has a largely cystic appearance. **B**, Microscopic appearance of the two components.

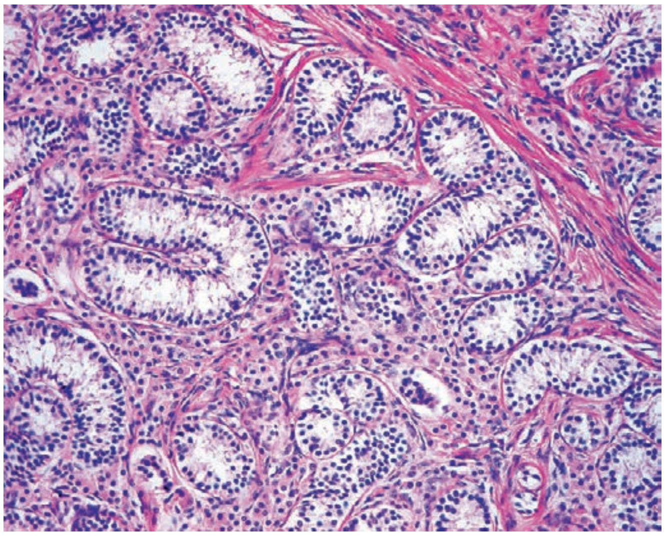

Figure 35.3 Immature testicular tubules in testicular feminization syndrome.

of the eventual occurrence of malignant tumors in the cryptorchid testes of approximately 9% of these patients. For this reason, the testes should be removed after puberty and supplemental estrogen therapy given. A classification of disorders of sexual development is presented in Table 35.1.

Cysts, Stromal Hyperplasia, and Other Non-Neoplastic Lesions

Ovarian diseases of surgical importance can be broadly divided into non-neoplastic cysts, inflammations, and neoplasms. Non-neoplastic cysts are sufficiently common as to be the norm during the reproductive years; cysts up to 6 cm, detected by ultrasound, can be followed and most will resolve spontaneously, reflecting their functional nature.

Inclusion cysts ("cortical inclusion cysts") are common in older women; they are generally small and multiple and have no clinical significance. Most of them probably arise from invaginations of the surface epithelium, with subsequent loss of the connection with the surface (Fig. 35.4A).[33] Microscopically, they are lined by a flattened, cuboidal, or columnar epithelium; tubal metaplasia is frequent (see Fig. 35.4B). Psammoma bodies may be seen in their lumen or in the adjacent stroma. By definition cortical inclusion cysts are less than 1 cm and if larger they are considered to be serous cystadenomas, if there is tubal epithelium, or benign simple cysts if lined by nondescript flattened or cuboidal epithelium. This rule need not be firmly adhered to; in general, if a cyst is clinically evident it can be designated a cystadenoma or benign simple cyst, while a small cyst that is an incidental finding can be designated an inclusion cyst. This practice reflects the arbitrary nature of the definitions, with a continuum existing between inclusion cyst and serous cystadenoma.

Follicular cysts form by distention of developing or atretic follicles and usually do not exceed 10 cm in diameter (Fig. 35.5). It has been proposed that cystic follicular structures be designated as (normal) *cystic follicles* when measuring less than 2.5 cm and as *follicular cysts* when exceeding this diameter. The latter may occur at any age from infancy to menopause and are asymptomatic in the majority of cases. Occasionally, twisting of the pedicle occurs, with resulting hemorrhagic infarction of the ovary. In children, the cysts may be seen in conjunction with precocious puberty.[34,35] During reproductive life, they may be associated with endometrial hyperplasia and metrorrhagia.[36] The cyst fluid may contain estrogens.

The cyst wall is lined by theca, with or without an inner granulosa layer (Fig. 35.6). The theca layer is frequently luteinized. The granulosa layer may be luteinized after puberty but not before. **Multiple luteinized follicular cysts** (theca–lutein cysts; hyperreactio luteinalis) are common in cases of hydatidiform mole and choriocarcinoma but also have been seen in twin pregnancies and, exceptionally, in uncomplicated single pregnancies (Fig. 35.7).[37] **Large solitary luteinized follicular cyst** is a rare lesion presenting during pregnancy and puerperium, unaccompanied by endocrine abnormalities. The median diameter of this type of cyst is 25 cm.[38] Marked focal atypia is often seen in the luteinized cells of this lesion.[39]

Polycystic (sclerocystic) ovaries are characterized by multiple follicular cysts or cystic follicles with varying degrees of luteinization of the theca interna, and dense fibrosis of the superficial cortex. Evidence of previous ovulation (i.e. corpora lutea or albicantia) is sparse or absent (Fig. 35.8).[40,41] Various clinical manifestations may develop in patients with polycystic ovaries, including amenorrhea and sterility, endometrial hyperplasia, and frank virilism; these fall under the collective designation of polycystic ovary syndrome (PCOS), formerly (and still occasionally) referred to as Stein–Leventhal syndrome. The pathogenesis of PCOS is poorly understood.[38,42–43] These patients have "masculinizing" pituitary and ovarian responses to stimulation by the specific gonadotropin-releasing hormone agonist nafarelin, suggesting that the regulation of the ovarian 17-hydroxylase and C-17,20-lyase activities is abnormal.[44] Dysregulation of 11β-hydroxysteroid dehydrogenase, causing increased oxidation of cortisol to cortisone, has also been documented.[45]

Table 35.1 Disorders of sexual development

							HORMONES			
SYNDROME	**GONAD**	**DUCTS**	**EXTERNAL GENITALIA**	**PUBERTY**	**BARR**	**CHROMOSOMES**	**FSH**	**17-KS**	**ESTROGEN**	**REMARKS**
Klinefelter	Testis with hyalinized sclerotic tubules and clumped Leydig cells	Male	Male	Normal penis with small testes; partial androgen lack	“True” are chromatin positive, a few are 2+ or 3+	All chromatin positive have 2 Xs and a Y in at least some cells. Chromatin negative are 46,YY	↑↑	N or ↑	N	Affects 1:400 newborn males
Turner	Streak gonad with whorled stroma	Female	Female	No pubertal development; rare cases show mild virilization	50% chromatin negative	Second sex chromosome missing or abnormal in some or all of the cells	↑↑	↓	↓	1:7000 newborns, more common in abortuses; short stature
True hermaphrodite	Ovary and testis	All have uterus, most have tubes too, a few have vasa	Ambiguous but 80% favor the male	80% have gynecomastia, 50% menstruate	80% chromatin positive	60% are 46,XX in blood cells only; Y present in most of the others	N	N	N	—
Mixed gonadal dysgenesis	Streak plus testis or tumor	Female; vas found occasionally	Vary from female (often with clitoromegaly) to male with hypospadias to normal male	Virilization, sometimes complete; breast development only with tumors	Chromatin negative	Almost all are mosaics including XO stem; many have Y-bearing stem as well	↑	N	?	—
Dysgenetic male pseudohermaphroditism	Dysgenetic testis	Mixed male and/or female	Variable virilized	Rarely patients may be fertile	Chromatin negative	Some are XO/XY	↑	N	?	—
Familial male pseudohermaphroditism that ranges from testicular feminization to	Immature infertile testis	No uterus, ± rudimentary vas	Female with short, blind vagina	Breasts develop but sexual hair is missing	Chromatin negative	46,XY	↑ or N	↑ or N	N	Sex-linked recessive or sex-limited autosomal dominant
Reifenstein syndrome	Infertile testis	Male	Male with hypospadias ± cleft scrotum	Androgen lack is evident in incomplete virilization	Chromatin negative	46,XY	↑ or N	↑ or N	?	
Female Pseudohermaphroditism										
1. Congenital adrenal hyperplasia	Ovary	Female	Variably virilized	Amenorrhea with virilization	Chromatin positive	46,XX	N	↑↑	N	Autosomal recessive
2. Nonadrenal	Ovary	Female	Variably virilized	Normal	Chromatin positive	46,XX	N	N	N	Consider maternal exposure to progestins or androgens

↑, Increased; ↑↑, markedly increased; ↓, decreased; *N,* normal.
The summaries under the several headings are necessarily brief; the text should be consulted for details, qualifications, and crucial exceptions.
From Federman DD. *Abnormal Sexual Development. A Genetic and Endocrine Approach to Differential Diagnosis*. Philadelphia: WB Saunders; 1967.

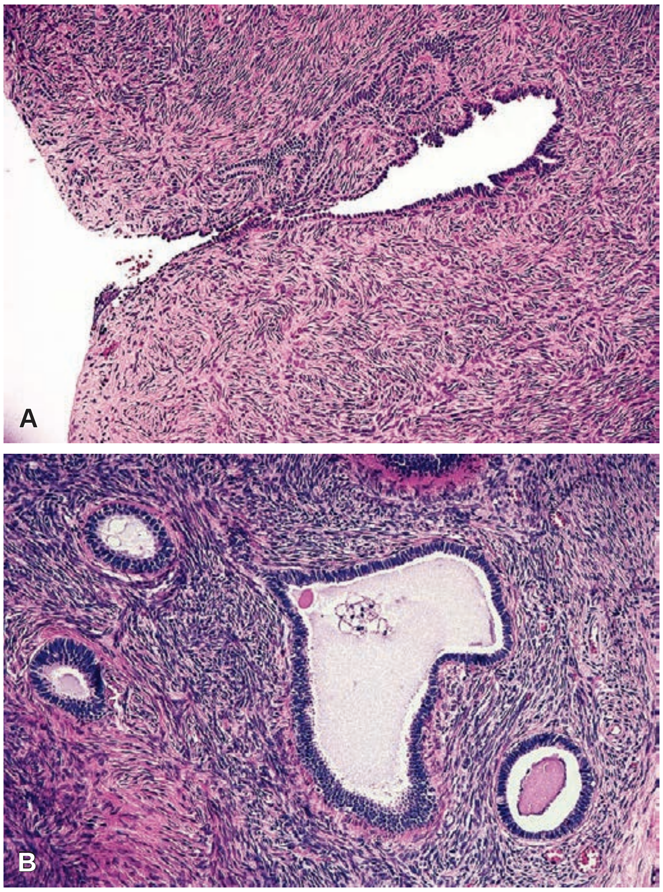

Figure 35.4 Ovarian Inclusion Cysts. A, Cyst being formed through invagination of the surface epithelium. **B**, Multiple inclusion cysts within ovarian cortex. The lining is similar to that of the surface epithelium but tends to be taller and more prominent.

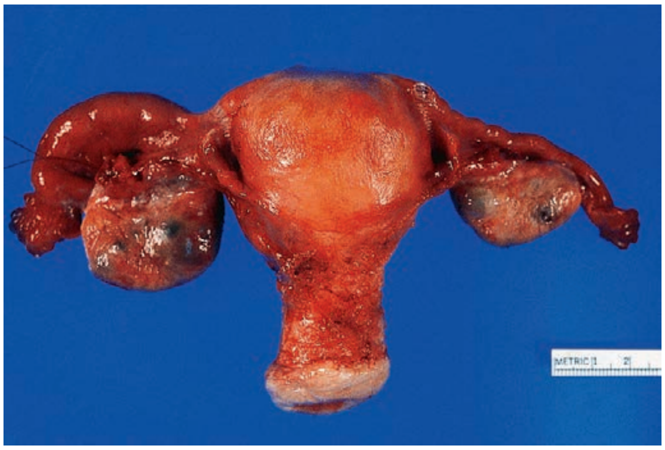

Figure 35.5 Outer appearance of bilateral ovarian follicular cysts.

In general, the ovaries of patients with PCOS have the macroscopic and microscopic features of polycystic ovaries just described. The histologic appearance does not correlate well with clinical manifestations in a given patient, and sclerocystic changes can be seen as an incidental finding in asymptomatic patients whose ovaries are removed for unrelated reasons. Polycystic ovaries have also been observed in association with primary hypothyroidism.[46]

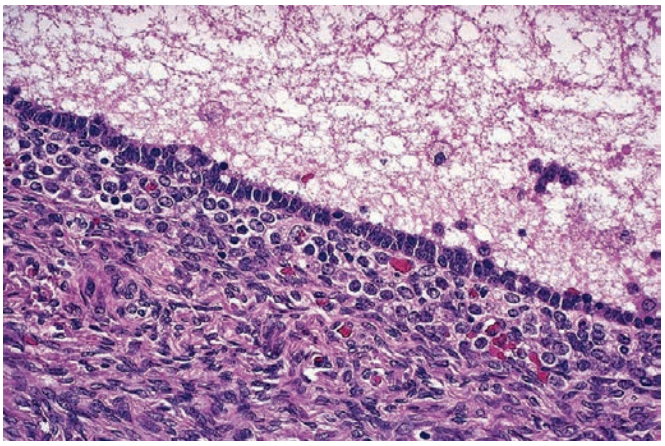

Figure 35.6 Microscopic Appearance of Follicular Cyst. A single layer of granulosa cells is resting on a thick theca layer.

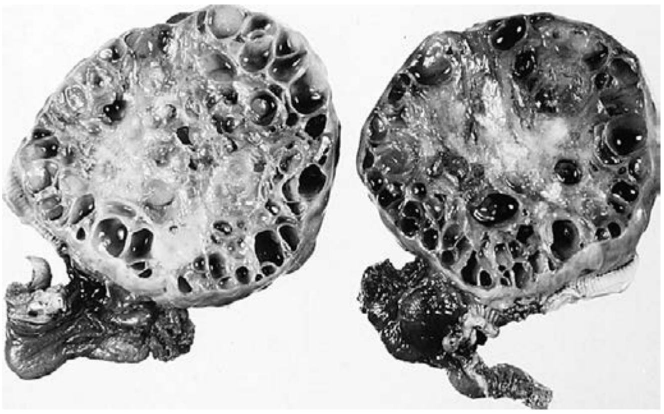

Figure 35.7 Marked bilateral ovarian enlargement due to multiple theca–lutein cysts associated with normal pregnancy. The changes were misinterpreted as representing neoplasms and both ovaries were excised.

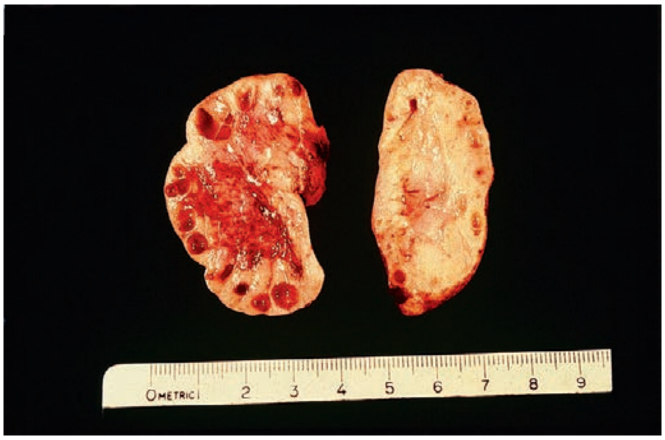

Figure 35.8 Outer aspect and cut surface of ovary in a patient with polycystic ovary syndrome. Note the numerous follicular cysts beneath the ovarian surface and the absence of corpus luteum.

Most patients with PCOS will respond favorably, with restoration of the menstrual cycle, to medical treatment, typically metformin (an oral hypoglycemic agent) and an aromatase inhibitor such as letrazole.[47,48] The endometrium of patients with PCOS may become hyperplastic, and endometrial carcinoma may develop against this

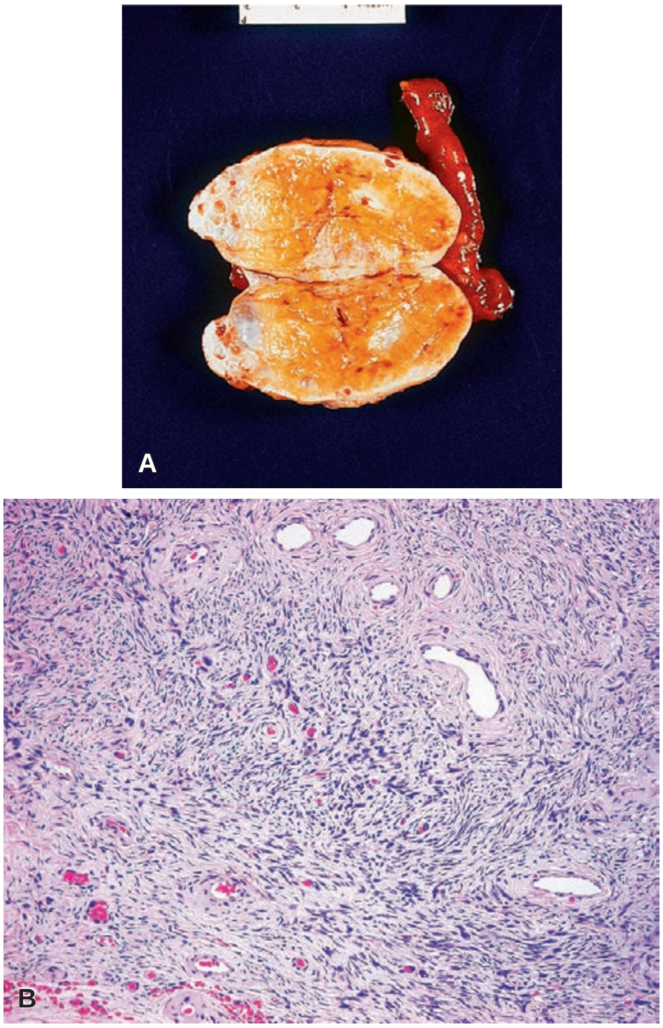

Figure 35.9 **Ovarian Stromal Hyperplasia. A**, Gross appearance. The cut surface is solid and has a yellowish hue. **B**, Microscopic appearance. The ovarian stroma is hypercellular.

background, the tumor typically being well differentiated and superficial.[49,50]

Stromal hyperplasia and hyperthecosis is characterized by a diffuse or nodular proliferation of plump ovarian cortical stromal cells encroaching on the medulla (Fig. 35.9).[7] Ovaries involved by stromal hyperplasia typically measure more than 5 cm in greatest dimension. Patchy luteinization of these cells may be present, a finding termed *stromal hyperthecosis*. Stromal hyperplasia and hyperthecosis may be associated with estrogenic or androgenic effects, obesity, hypertension, and an abnormal glucose tolerance test or even frank diabetes. The onset of symptoms may be abrupt, thus simulating a virilizing ovarian tumor. Immunohistochemical studies have shown androgen production by the luteinized stromal cells, suggesting that estrogenic effects in these cases are mediated through peripheral aromatization of these androgens.[51]

The boundaries between polycystic disease and stromal hyperplasia are ill-defined (Fig. 35.10)[41,52]; however, typical stromal hyperplasia lacks cysts and is usually more refractory to therapy.

Corpus luteum cysts are single and usually less than 6 cm in diameter. They may develop at the end of the menstrual cycle or may occur in pregnancy (Fig. 35.11). The cyst wall is composed of luteinized granulosa and theca cell layers. Hyaline bodies and foci

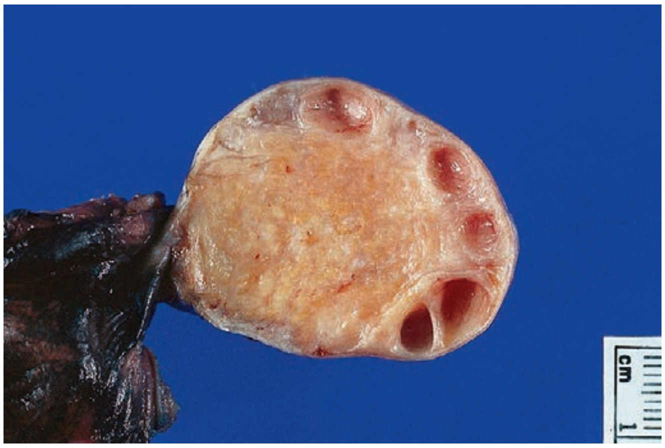

Figure 35.10 Ovary showing a combination of multiple follicular cysts and stromal hyperplasia, providing support for a pathogenetic link between the two processes.

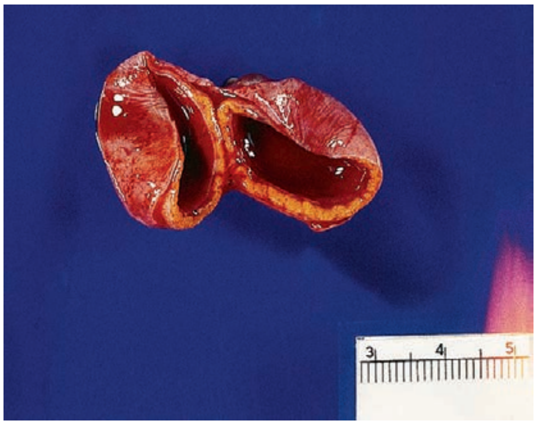

Figure 35.11 **Gross Appearance of Corpus Luteum Cyst.** The luminal content is typically hemorrhagic.

of calcification may be found in the cysts associated with pregnancy. The fluid content is often bloody. If the cyst ruptures, hemorrhage into the peritoneal cavity occurs (sometimes over 500 mL), and an erroneous diagnosis of ruptured ectopic pregnancy may be made.[53] It should be remembered that the corpus luteum is normally a cystic structure. The arbitrary diameter of 2.5 cm has been proposed to distinguish the (normal) *cystic corpus luteum* from a *corpus luteum cyst*, in a manner analogous to that employed for follicle-related cystic formations. Distinction between a corpus luteum cyst and a luteinized follicular cyst can be arbitrary; the former diagnosis is favored when the degree of luteinization is similar to that of the cells in a normal corpus luteum.

Ectopic decidual reaction can occur in the ovary during pregnancy and occasionally even in the absence of current or recent pregnancy.

So-called **luteomas of pregnancy** are yellow or orange solid nodules that may reach sizable proportions (Fig. 35.12).[39] They have been typically encountered during cesarean section in multiparous women, sometimes accompanied by a mild degree of virilization.[54,55] If left undisturbed, they will regress after delivery.[56] Microscopically, the lesions are composed of masses of uniform theca–lutein cells (Fig. 35.13). Occasionally, there is an associated granulosa cell proliferation.[57] All of the reported lesions have been benign. It is reasonable to regard them as nodular hyperplasias of theca–lutein

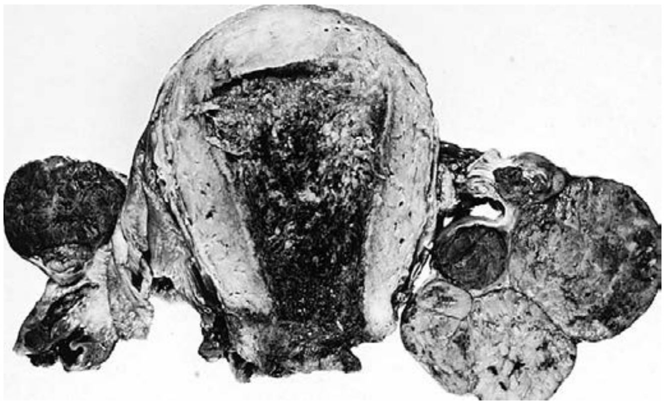

Figure 35.12 Bilateral pregnancy luteomas in a 29-year-old woman that were discovered incidentally at the time of cesarean section performed for cord prolapse. The tumors bled excessively on manipulation by the surgeon and had to be removed.

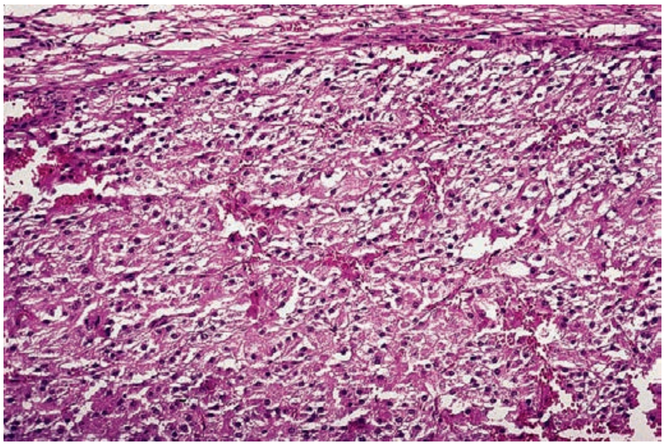

Figure 35.13 Solid growth pattern of pregnancy luteoma.

cells rather than true neoplasms.[55] If pregnancy luteoma is correctly identified by frozen section, no further surgery is necessary. A steroid cell tumor should not be diagnosed based on frozen section of an ovarian mass performed at the time of C-section as it is more likely to be a luteoma of pregnancy, and an incorrect diagnosis of steroid cell tumor may lead to an unnecessary oophorectomy. This scenario illustrates, as well as any example, the importance of having adequate clinical history at the time of intraoperative consultation/frozen section.

Developmental cysts derived from wolffian (mesonephric) and müllerian (paramesonephric) remnants are common in the region of the ovarian hilus. Suffice it to say here that, according to some authors, it is possible to distinguish these two types of tissue—and sometimes the cysts derived from them—on microscopic grounds.[58] Wolffian structures are lined by cuboidal, predominantly nonciliated epithelium resting on a well-developed basement membrane; müllerian formations are lined by generally taller, ciliated and nonciliated epithelium with larger nuclei and resting on an inconspicuous basement membrane. Such a distinction is not clinically important and may not be possible in some cases, and the designation of "Benign parovarian (or paratubal) cyst" may be used. Both may have a smooth muscle coat. According to these criteria and some ultrastructural differences,[59] **hydatids of Morgagni** (pedunculated cysts at the fimbriated end of the fallopian tube) are believed to be of müllerian origin, whereas most **parovarian** and **paratubal cysts** (in the tubo-ovarian ligament) and **Gartner duct cysts** (in the vaginal wall) are thought to arise from wolffian remnants.

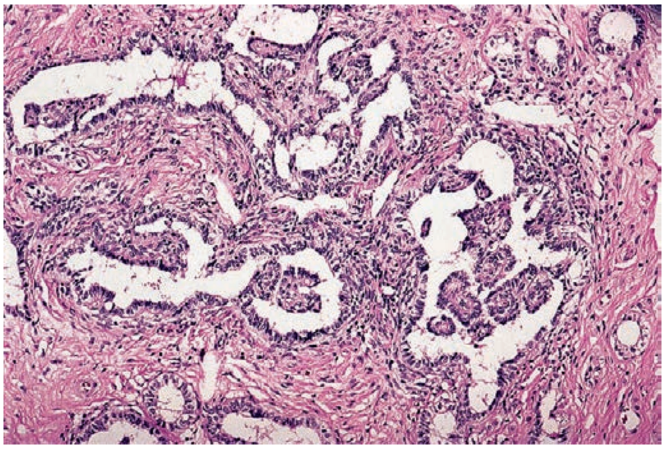

Figure 35.14 Benign hyperplastic changes in rete ovarii. This alteration is of no clinical significance.

Cysts of the rete ovarii are characterized by a hilar position, an epithelial lining of variable height that is usually nonciliated, crevices along the inner surfaces, and a fibromuscular wall that often contains hyperplastic hilus cells.[50] The rete ovarii may also be the site of benign proliferative lesions that have been variously reported as adenomatous hyperplasia[60] and adenoma (Fig. 35.14).[61]

Epidermoid cysts, lined by benign squamous epithelium without evidence of skin adnexal structures or other teratomatous elements, are exceptionally rare and are of uncertain histogenesis.[62–64]

Squamous metaplasia of the OSE accompanied by subjacent fibrosis has been described in patients on long-term peritoneal dialysis.[65]

Amyloidosis can exceptionally present in the form of bilateral ovarian masses.[66]

Supernumerary ovaries are extremely rare.[67] Most of the reported cases have measured less than 1 cm. They should be distinguished from **accessory ovaries**, which are small portions of ovarian tissue situated near—and sometimes connected to—the normally placed organ.[68]

Inflammation

Nonspecific inflammation of the ovary usually spreads from the endometrium and is practically always associated with tubal involvement. A large, loculated cystic mass filled with pus or secretion is often the result, the ovarian stroma forming part of the cystic wall (tubo-ovarian abscess or cyst). Exceptionally, a solid mass rich in foamy macrophages develops in long-standing cases (*"xanthogranulomatous oophoritis"*).[69,70]

Granulomatous infections such as tuberculosis occur in the ovary. Invariably this is hematogenous in origin and often also involves the tube and endometrium. In time, the infection may subside and leave a large tubo-ovarian cystic mass. Other infectious agents responsible for granulomatous oophoritis are *Actinomyces* (particularly common after the introduction of intrauterine devices), *Schistosoma*, and *Enterobius vermicularis*. Rarely, *sarcoidosis* and *Crohn disease* involve the ovary, the latter as a result of direct extension from the bowel. *Foreign body granulomas* can occur in the ovarian surface secondarily to talc, cornstarch, carbon pigment (at the site of fulguration surgery),[71] other foreign materials,[72] and keratin; the latter may originate from a ruptured ovarian cystic teratoma or may have spilled through the fallopian tube from an endometrial

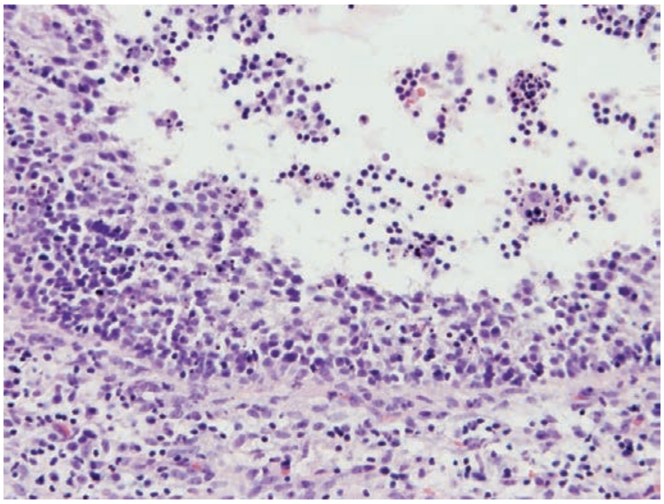

Figure 35.15 Lymphocytic and plasmacytic infiltrate of a developing follicle in autoimmune oophoritis.

adenocarcinoma of endometrioid type, with squamous differentiation.[73] *Palisading granulomas* of unknown etiology have also been reported, most of them in patients with a history of previous pelvic surgery.[74]

Autoimmune oophoritis is a poorly understood cause of premature ovarian failure characterized microscopically by lymphocytic and plasma cell infiltration in relation to developing follicles but not primordial follicles (Fig. 35.15).[71,75] It results in primary ovarian failure with either primary or secondary amenorrhea.[76,77] Many of the reported cases have been associated with adrenal failure (Addison disease), hypothyroidism, or both conditions.[76,78]

Eosinophilic perifolliculitis is characterized by a predominantly eosinophilic infiltrate around the follicles; it is not clear how this rare disorder relates to autoimmune oophoritis.[79]

Giant cell arteritis occasionally involves the ovary of elderly women; it may occur as an isolated finding (most frequently) or as a component of generalized giant cell arteritis.[80]

Endometriosis

The ovary is the most common site of endometriosis, as defined by the presence of endometrial glands *and* stroma outside the uterus.[81] The pathogenesis of endometriosis remains incompletely understood; suffice it to say that endometriosis shows evidence of clonality and in a minority of cases the epithelium has an activating KRAS mutation.[82,83] Ovarian endometriosis is usually associated with infertility, and it remains active during the childbearing years.[84,85] Pain associated with the menstrual cycle is the most common symptom; infrequently, the disease is complicated by massive ascites or perforation into the peritoneal cavity.[86] Grossly, it usually presents as small, slightly raised, blueberry-like spots on the ovarian surface, often accompanied by fibrous adhesions. In cases with extensive involvement, the entire ovary may be converted into a "chocolate cyst" as a result of repeated hemorrhages (Fig. 35.16). Microscopically, the typical lesions are composed of endometrial glands, endometrial stroma, and fresh and old (hemosiderin-containing) hemorrhagic foci (Fig. 35.17).[87] The endometrial stroma is responsible for the bleeding; it has cells with a "naked nucleus" surrounded by reticulin and typical spiral arterioles, in conjunction with old and recent hemorrhage. Unfortunately, this diagnostic combination of findings is not always present. The more advanced the endometriotic lesion, the more difficult the diagnosis and the greater the number of sections required to make it. Not infrequently, the repeated hemorrhages have totally destroyed the endometrial tissue, the cyst being lined by several layers of hemosiderin-laden macrophages with a thick fibrous wall. Under these circumstances, the most the pathologist can do is to report the case as a hemorrhagic cyst and comment that the changes are "consistent" with those of endometriosis. Sometimes, the lesion is entirely composed of *necrotic pseudoxanthomatous nodules*, to be distinguished from infectious granulomas and necrotic neoplasms (Fig. 35.18).[88] Other morphologic variations of endometriosis include the formation of Liesegang rings,[89] stromal elastosis,[90] and smooth muscle hyperplasia,[91] the latter sometimes resulting in the formation of uterus-like masses.[92]

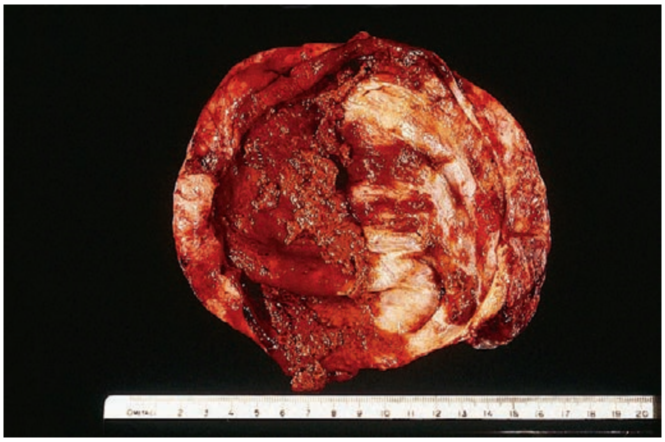

Figure 35.16 Inner surface of cyst in a case of ovarian endometriosis. The color is typically brown.

The ectopic endometrial tissue of endometriosis is subject to most of the influences that affect the intrauterine endometrium. Ovarian endometriosis more often undergoes malignant transformation than endometriotic foci elsewhere in the pelvis. Somewhat confusingly, two different premalignant changes have been described within ovarian endometriosis, and both have been termed "atypical endometriosis." The first consists of cells that do not show significant stratification but which have prominent nuclear atypia (Fig. 35.19).[93–96] These cells are thought to be a precursor of clear cell carcinoma and can have ARID1A mutations and show an immunophenotype intermediate between endometriosis and clear cell carcinoma.[97] The other premalignant change seen in ovarian endometriosis is morphologically identical to atypical endometrial hyperplasia, with glandular crowding and atypia.[98] This is thought to be the precursor of endometrioid carcinoma. Although clear cell and endometrioid carcinomas account for most malignancies arising in endometriosis, a wide range of other malignancies may also be encountered in association with ovarian endometriosis (e.g. carcinosarcoma, adenosarcoma, endometrial stromal sarcoma, seromucinous borderline tumor, and, rarely, serous borderline tumor or low-grade serous carcinoma).

Tumors

Classification

The classification of ovarian tumors is primarily morphologic and based on the cytologic features of the tumor cells. This approach has served us well over the years, with recent molecular studies, for the most part, supporting this morphology-based classification system and demonstrating that it accurately reflects both histogenesis/cell of origin, and the underlying molecular abnormalities of the different

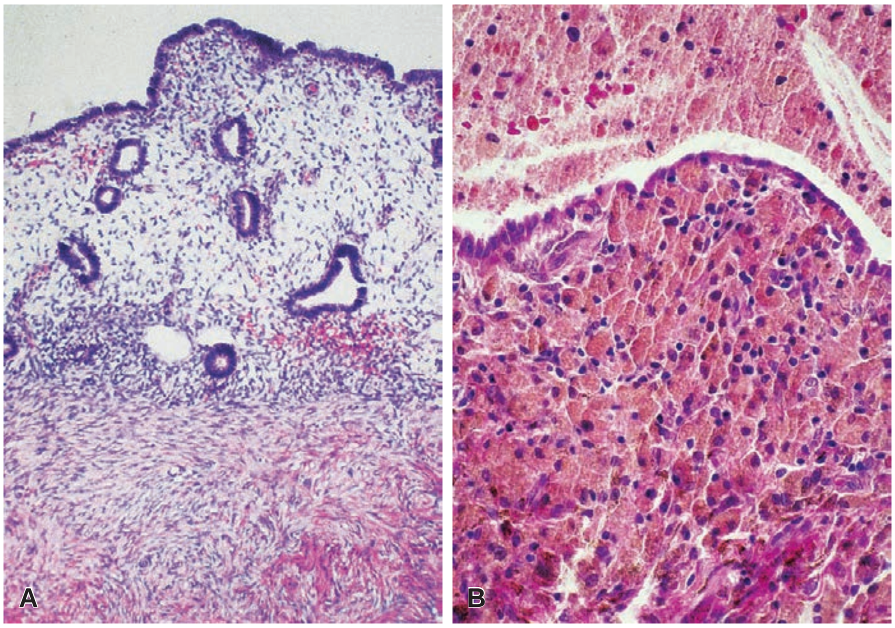

Figure 35.17 **Ovarian Endometriosis. A,** In this area endometrial tissue faithfully reproduces the appearance of normal endometrium, in terms of both glands and stroma. **B,** A more common appearance resulting from repeated hemorrhage and accumulation of hemosiderin-laden macrophages.

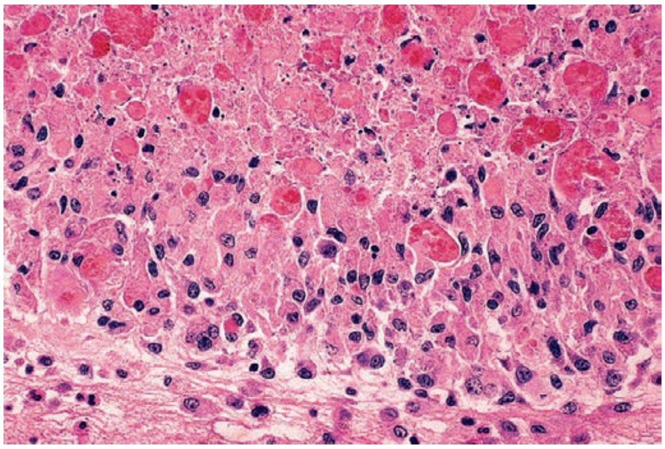

Figure 35.18 Necrotic nodule surrounded by histiocytes in pelvic endometriosis.

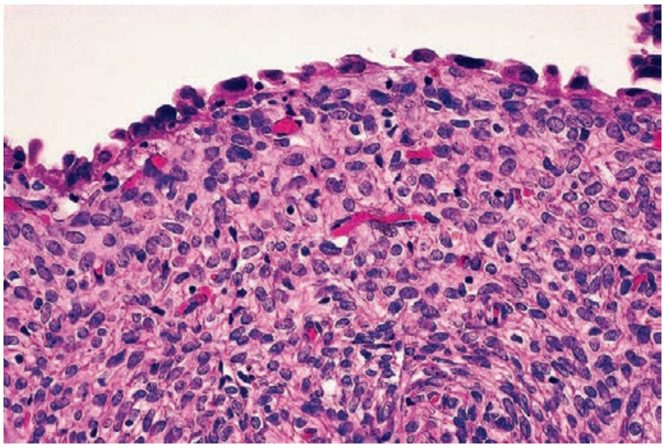

Figure 35.19 Atypia of the cells lining an ovarian endometriotic cyst, a change referred to as atypical endometriosis.

ovarian tumor subtypes.[99] While there have been some minor adjustments made, reflected in the 2014 WHO classification system,[100] the fundamental premise that the ovary contains four major types of tissue, all of which can give rise to a variety of neoplasms, has remained unchanged for decades. These four tissue types are:

1. Epithelium
2. Germ cells
3. Sex cords
4. Ovarian stroma, specialized and nonspecific.

Epithelial Tumors

Overview

Epithelial tumors, numerically the most important group of neoplasms, have traditionally been thought to derive from the OSE[101] and were thus referred to as "surface epithelial" tumors. It is now appreciated that the epithelial tumors of the ovary are of diverse origins, histogenetically, and the cell of origin of each histotype will be discussed in the section devoted to that specific histotype, later in this chapter.

Epithelial ovarian tumors are subclassified based on cell type as **serous, endometrioid, clear cell, mucinous, seromucinous,** or **transitional (Brenner)**.[100] It is now appreciated that the histotype reflects differences in cell of origin and molecular abnormalities, and subclassification based on cell type, or histotype, has taken on increased importance in recent years.[100]

Within each histotype, tumors are further subclassified as **benign, borderline,** or **malignant.** Benign tumors are characterized by epithelium with benign nuclear features and differentiated cytoplasm; for example, the benign serous tumors feature cells with cilia, morphologically identical to the normal ciliated cells of the fallopian tube. Benign epithelial tumors can be further subclassified based on whether they are predominantly cystic, cystic and solid, or predominantly solid with fibromatous stroma, as cystadenoma, cystadenofibroma, and adenofibroma, respectively.[99] There is an arbitrary cutoff between cystadenoma and cystadenofibroma, with the latter having at least 25% solid component. This subclassification based on the gross appearance of the tumor is not clinically relevant, beyond allowing correlation with radiologic findings.

The borderline category is characterized by cytologic atypia, but without evidence of invasion, and its existence as a diagnostic entity has been controversial. Although it has been stated that this category is unique to ovarian tumors, other "borderline" tumors do exist, such as low-grade mucinous neoplasm of the vermiform appendix. Attempts have been made to eliminate the borderline category of ovarian epithelial tumors, so that tumors are classified as either benign or malignant[102,103]; however, the borderline category has survived these attempts. The key to the survival of "borderline" as a diagnostic entity can probably be found in its history as a subcategory of ovarian epithelial tumors[104]; it was recognized that there were advanced-stage tumors that did not behave like usual high-stage ovarian carcinoma, and in these patients adjuvant treatment did more harm than good. Creation of a borderline designation for these unusual tumors allowed for a more conservative management to emerge. This is true specifically for serous and seromucinous borderline tumors, where a significant minority of cases (15%–40%) are associated with extra-ovarian implants (i.e. stage II or III), and yet there is a favorable prognosis. Although the borderline category has been extended to the other ovarian histotypes (e.g. clear cell, endometrioid), such tumors are invariably stage I and can be expected to behave in a benign fashion when diagnosed using strict criteria.

The distinction between borderline and malignant is based on the presence of "invasion" in the latter; the criteria for invasion differ from histotype to histotype, and histotype-specific discussions are provided later in this chapter. The malignant epithelial tumors ("carcinomas") show other striking differences between histotypes, which are summarized in Table 35.2,[105] and described in more detail in the histotype-specific sections of this chapter, later. It is important to recognize that although histotype of ovarian carcinoma was considered to not be diagnostically reproducible or clinically relevant in the past, that has changed, and ovarian carcinoma histotype can be diagnosed with very high interobserver agreement[106–108] and increasing clinical significance. There remain 1%–2% of ovarian carcinomas that show unusual morphologic features and defy histotype assignment, but in most tumors the diagnosis of histotype is straightforward on routine H&E stains. The importance of histotype in ovarian carcinoma can be illustrated by consideration of two aspects of ovarian carcinoma: stage at presentation and association with hereditary cancer susceptibility syndromes.

The stage at presentation of ovarian carcinoma of different histotypes are shown in in Table 35.3.[109] For patients presenting with high-stage disease (i.e. stage III or IV), the large majority are high-grade serous, while patients presenting with tumors confined to the adnexa are more likely to have a tumor other than high-grade serous carcinoma (HGSC), which account for a minority of such cases. The histotype of organ confined ovarian carcinomas, e.g. presenting at the time of frozen section for an adnexal mass that was thought to be an endometriotic cyst preoperatively, are very different than those diagnosed in patients with ascites and omental involvement.

Familial Ovarian Cancer Syndromes

There are two common autosomal dominant hereditary cancer syndromes: hereditary breast and ovarian cancer syndrome (HBOCS) and Lynch syndrome, with the former first described by Henry Lynch and the latter named after him for his pioneering work in establishing

Table 35.2 Features of the five major histologic types of ovarian carcinoma.

	HGSC	CCC	EC	LGSC	MC
Mean age	63	55	58	53	45
5-Year survival (stage III only)	40	23	66	71	NA
Origin	Fallopian tube	Endometriosis	Endometriosis	Cystadenoma	Germ cell, transitional epithelium
Molecular abnormalities	Genomic instability; TP53 mutation; homologous recombination DNA damage repair defects; CCNE1, NOTCH3 activation; Rb, NF1 inactivation	Wnt-catenin activation; ARID1A-chromatin remodeling complex inactivation; PI3K activation; PTEN inactivation, MMR abnormalities		KRAS/BRAF/MEK pathway activation	ERBB2/KRAS/BRAF/MEK pathway activation
Inherited syndromes	HBOC	LS	LS	?LS	?LS
Sensitivity to platinum-based chemotherapy	Sensitive	Relatively resistant	Relatively resistant	Relatively resistant	Relatively resistant
Adjuvant/targeted therapies licensed or in trial	PARPi; immune checkpoint inhibitors	Radiotherapy; Sunitinib	mTOR inhibitors	Selumetinib (MEK1/2 inhibitors)	Trastuzumab

CCC, Clear cell carcinoma; *EC*, endometrioid carcinoma; *HBOC*, hereditary breast and ovarian cancer syndrome; *HGSC*, high-grade serous carcinoma; *LGSC*, low-grade serous carcinoma; *MC*, mucinous carcinoma; *LS*, Lynch syndrome; *NA*, not applicable.

From Singh N, Gilks CB. The changing landscape of gynaecological cancer diagnosis: implications for histopathological practice in the 21st century. *Histopathology*. 2017;70:56–69.

Table 35.3 Low-stage (I/II) versus high-stage (III/IV) distribution of histotypes of epithelial ovarian cancer

OVARIAN CARCINOMA HISTOTYPE	PERCENTAGE (ALL STAGES) (%)	PERCENTAGE (STAGE III/IV) (%)	STAGE I/II: STAGE III/IV
High-grade serous	68.1	87.7	20:80
Clear cell	12.2	4.5	82:18
Endometrioid	11.3	2.5	88:12
Mucinous	3.4	1.2	82:18
Low-grade serous	3.4	5.3	18:82

From Singh N, McCluggage WG, Gilks CB. High-grade serous carcinoma of tubo-ovarian origin: recent developments. *Histopathology*. 2017 May 6. [Epub ahead of print].

the importance of these hereditary cancer syndromes; both are associated with an increased risk of ovarian carcinoma, but the histotypes of the carcinomas encountered in these syndromes are completely different. Germline mutations in BRCA1 or BRCA2, which encode proteins involved in high-fidelity repair of double-strand (DS) DNA breaks, account for 95% of cases of HBOCS, and these patients have an estimated 45% lifetime risk of developing ovarian carcinoma, although the risk varies depending on the specific mutation, being higher in patients with BRCA1 mutations than those with BRCA2 mutations.[110,111] In HBOCS, patients are at increased risk of developing HGSC but not at significantly increased risk of developing other histotypes of ovarian carcinoma, borderline tumors, germ cell tumors or sex cord–stromal tumors.[112,113] Of patients newly diagnosed with HGSC, 15%–20% will have a germline BRCA1 or BRCA2 mutation; consideration should therefore be given to genetic counseling and testing for HBOC in all such patients.[114]

Lynch syndrome, secondary to mutations in genes involved in another DNA repair pathway that is, mismatch repair, is associated with an 8%–10% lifetime risk of developing ovarian carcinoma,[115,116] and the carcinomas that arise in patients with Lynch syndrome are of those histotypes associated with endometriosis (i.e. endometrioid and clear cell).[117,118] The likelihood of a clear cell or endometrioid carcinoma of the ovary being associated with Lynch syndrome appears to be the same as that of colorectal carcinoma or endometrial carcinoma (i.e. 3%–5%). Therefore, if screening for Lynch syndrome mutations through immunostaining for mismatch repair enzymes in newly diagnosed carcinomas is being done, it has been suggested that it should be inclusive of not just colorectal and endometrial carcinoma, but the 20% of ovarian carcinomas of endometrioid or clear cell type.[118]

Serous Tumors

Serous tumors make up about one-fourth of all ovarian tumors and most occur in adults. A critical advance in our understanding of ovarian neoplasia is the recent recognition that low-grade serous neoplasms are a different disease than HGSC.[119–124] In the past it was thought that HGSCs arose through progression of low-grade serous neoplasms, but it is now recognized that, despite the shared "serous" or fallopian tube cell type, the low-grade and high-grade serous tumors are not closely related. Differences include cell and site of origin, molecular events during pathogenesis and response to chemotherapy, among others. Accordingly the low-grade and high-grade serous tumors will be discussed separately.

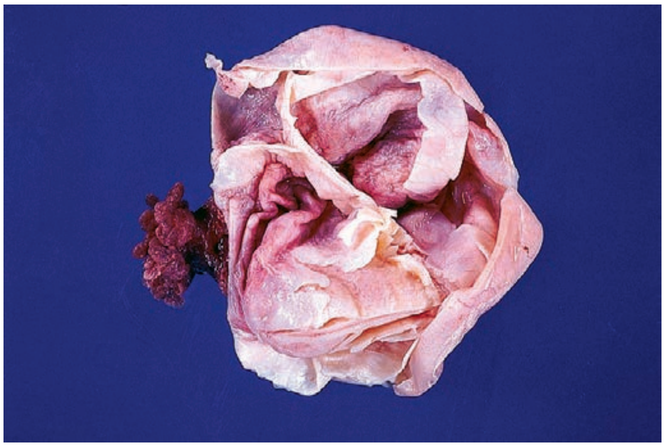

Figure 35.20 Smooth outer and inner surfaces of the cystic formations in a case of ovarian serous cystadenoma.

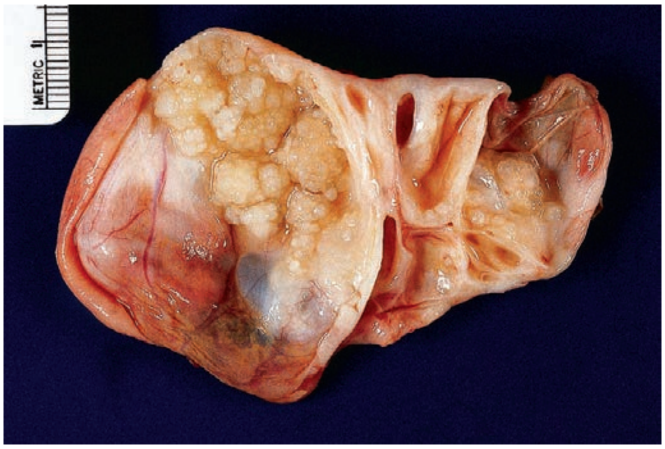

Figure 35.21 Inner aspect of serous cystadenoma showing papillary structures protruding within.

Low-Grade Serous Neoplasia

This category is inclusive of benign and borderline serous tumors and low-grade serous carcinoma. Grossly, these tumors typically consist of cystic masses, usually unilocular, containing a clear but sometimes viscous fluid (Fig. 35.20). Papillary formations are often present, most of them protruding into the cavity but some occasionally occur on the outer surface (Fig. 35.21). In serous borderline tumors the papillae lining cysts are more delicate than the predominantly stromal papillae of benign serous tumors (Fig. 35.22). The low-grade serous carcinomas tend to be solid but lack conspicuous areas of necrosis and hemorrhage.

Microscopically, cuboidal to columnar cells are seen lining the wall of the cysts and the papillae (Fig. 35.23). They are similar to normal tubal epithelium at both a light and electron microscopic level.[125] Hobnail cells can be present, not to be taken as evidence of the presence of a clear cell carcinoma component.[126] In borderline tumors and low-grade serous carcinomas, calcific concretions with concentric laminations (psammoma bodies) are often present.

A morphologic spectrum of proliferation exists in these tumors. At one end is the benign **serous cystadenoma**, in which the cysts

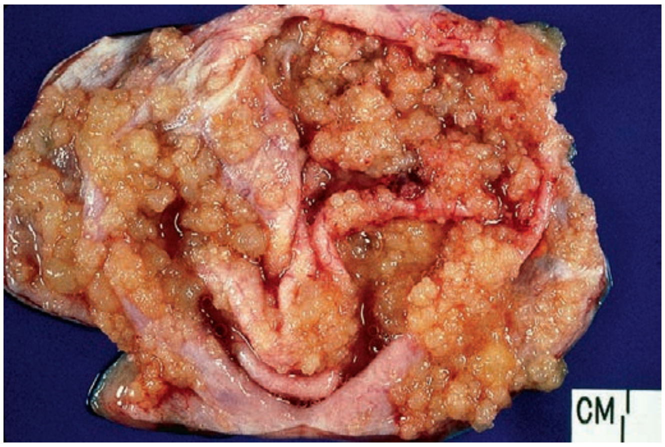

Figure 35.22 Inner aspect of an ovarian serous borderline tumor. Numerous fine papillary projections can be appreciated.

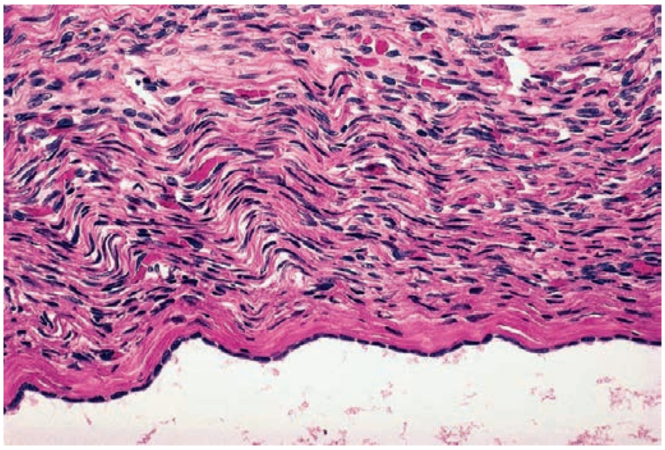

Figure 35.23 Single layer of bland-looking epithelial cells lining one of the cystic structures of a serous cystadenoma.

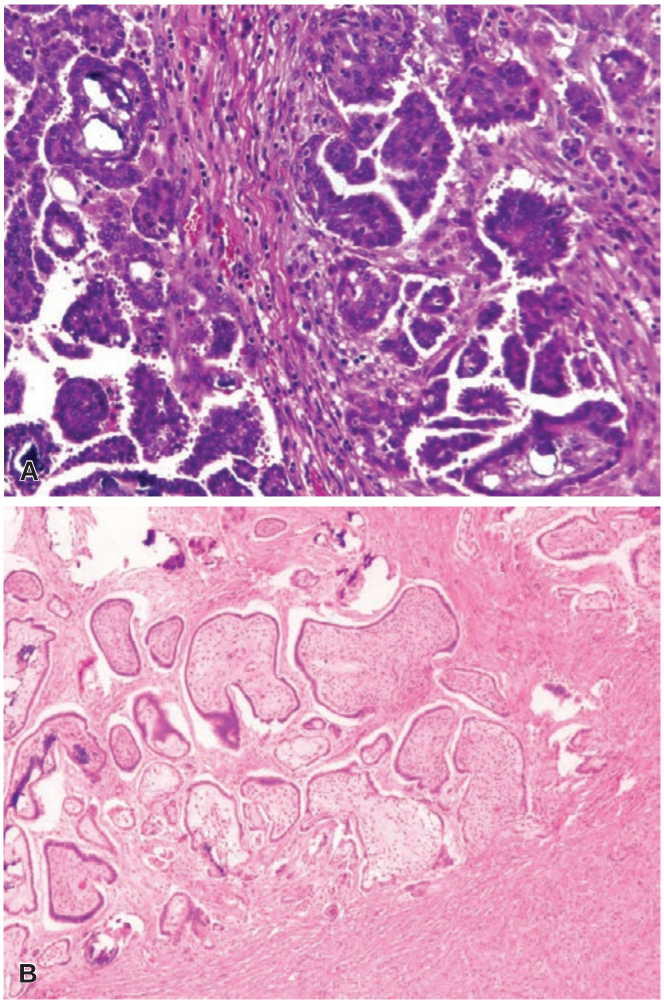

Figure 35.24 **Low-Grade Serous Carcinoma.** Invasion is evident as micropapillae and individual cells infiltrating the stroma **(A)** and as macropapillae, with broad central cores, also infiltrating the stroma **(B)**; note the clear space surrounding the invasive cell clusters.

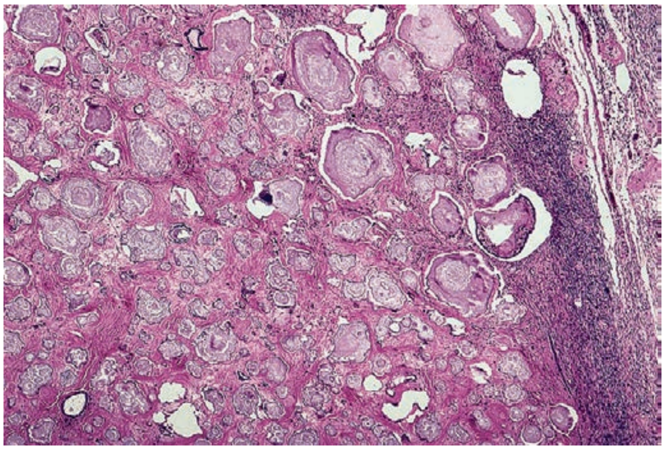

Figure 35.25 Low-grade serous carcinoma with innumerable psammoma bodies, so-called serous psammocarcinoma.

and the papillae (if present) are lined by a single layer of cells, without atypia, architectural complexity, or invasion (see Fig. 35.23). At the other end is low-grade serous carcinoma, characterized by low-grade nuclear atypia, mitotic activity, stratification, glandular complexity, branching papillary fronds, and *stromal invasion* (Fig. 35.24). Stromal invasion in low-grade serous carcinoma can show a number of patterns, which may be admixed in a single tumor,[127] and include: A. single cells and small, compact, irregular nests of cells, B. micropapillae and complex papillary forms (see Fig. 35.24A), C. inverted macropapillae, in which the neoplastic epithelium covers broad fibrovascular stromal stalks (this is the least common pattern; see Fig. 35.24B), D. cribriform, E, glandular or cystic, and F. solid sheets with slit-like spaces. In all of these patterns there is typically a clear space surrounding the neoplastic cells. **Serous psammocarcinoma**, so called, is a rare variant of low-grade serous carcinoma characterized by massive psammoma body formation (Fig. 35.25).[128] In between these two ends of the spectrum are serous borderline tumors, characterized by cellular stratification, detached cell clusters, atypia and occasional mitotic figures, but lacking stromal invasion (Fig. 35.26).[129,130] Borderline tumors account for approximately 15% of all serous tumors.[131–135] Ciliated cells are invariably present in benign serous tumors, less common in serous borderline tumors and uncommon in low-grade serous carcinoma.

In summary, benign serous tumors (serous cystadenoma, serous cystadenofibroma, or serous adenofibroma) are distinguished from

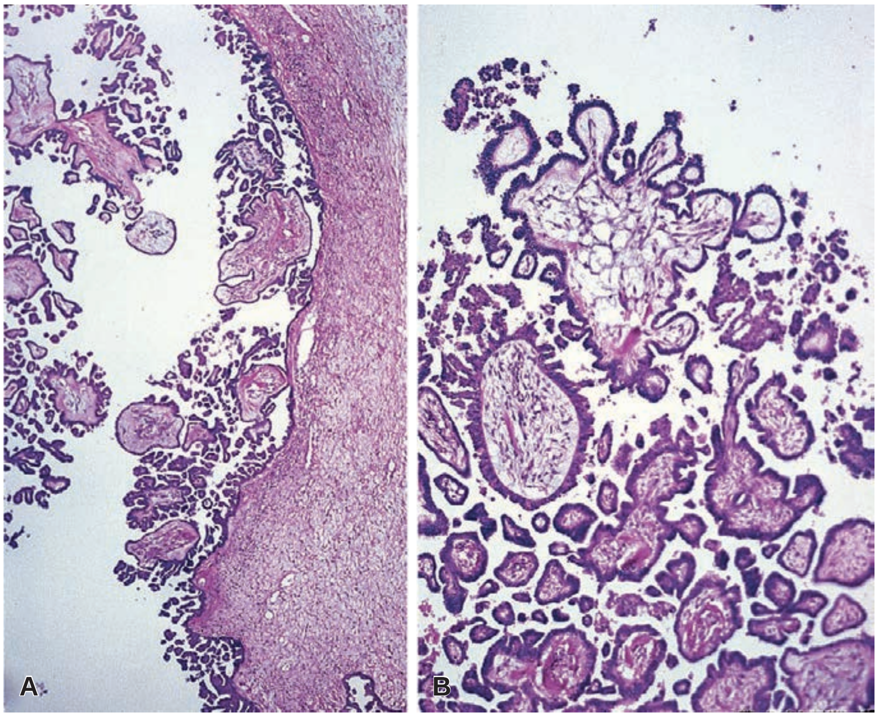

Figure 35.26 Low-power **(A)** and medium-power **(B)** appearance of ovarian borderline serous neoplasm. The growth is entirely exophytic.

serous borderline tumor by the absence of cellular stratification and atypia. The finding of detached clusters of epithelial cells is important evidence of cellular stratification; epithelial pseudostratification with apparent multilayered epithelium can be seen due to tangential sectioning, but this never leads to the presence of detached cell clusters. When the "borderline" features are present only focally (i.e. account for less than 10% of the cyst lining) in an otherwise benign tumor, the designation *"cystadenomas with focal proliferation or focal atypia"* can be used and these tumors also have a benign course.[131,136]

Borderline serous tumors are distinguished from low-grade serous carcinoma by the absence of stromal invasion. It should also be noted that microinvasion in serous borderline tumors, defined as one or more invasive foci measuring less than 5 mm in greatest dimension, is a relatively common finding in serous borderline tumor, seen in 10%–15% of cases, and is not of prognostic significance (Fig. 35.27).[100,137,138] The microinvasive foci typically appear as individual cells or clusters of cells with abundant eosinophilic cytoplasm ("eosinophilic metaplastic cells") that show a low Ki67 labeling index.[139,140] It should be noted that in 50% or more of low-grade serous carcinomas there is a coexisting borderline component, from which the low-grade serous carcinoma has presumably arisen. A special circumstance is when there is a serous borderline tumor of the ovary and invasive low-grade serous carcinoma in the extra-ovarian implants (a situation that in the past would have led to a diagnosis of "serous borderline tumor with invasive implants). Recognition of invasive carcinoma in extra-ovarian implants is based on the criteria proposed by Bell et al.[141]: the presence of a haphazard infiltrative growth pattern that destroys the architecture of the invaded tissues. Surface peritoneal involvement does NOT constitute evidence of invasion in extra-ovarian implants; there must be invasion into underlying tissue. The presence of invasion at extra-ovarian sites should lead to a diagnosis of low-grade serous carcinoma, even if the ovarian tumor is entirely borderline.[100,142]

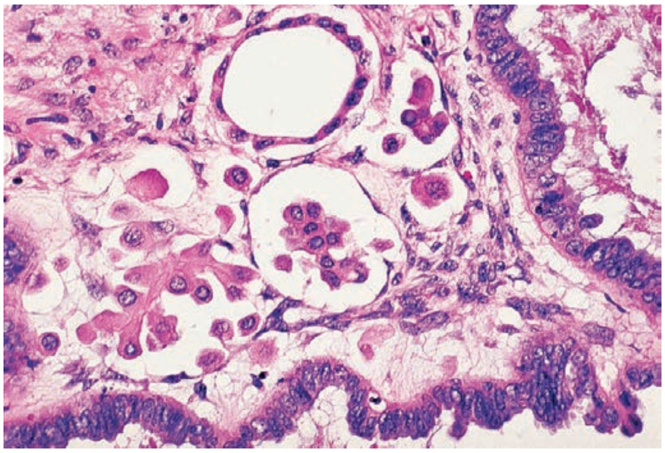

Figure 35.27 Serous borderline tumor with focal microinvasion represented by clusters of cells with abundant eosinophilic cytoplasm.

Low-grade serous carcinomas are distinguished from the much more common HGSCs by their frequent association with serous borderline tumor and a lesser degree of nuclear pleomorphism (less than threefold variation in nuclear size). In cases where there remains difficulty in deciding between these two possibilities, the low-grade serous carcinomas have a much lower mitotic rate than HGSCs (12 or fewer MF per 10 HPF),[119–121] and p53 immunostaining shows a normal pattern, compared to the abnormal staining (so-called all or nothing patterns) present in 95% of HGSCs.

Prognosis

The benign serous tumors are invariably benign, while the prognosis of serous borderline tumors is dependent primarily on stage. Stage Ia tumors, without surface involvement, positive washings or

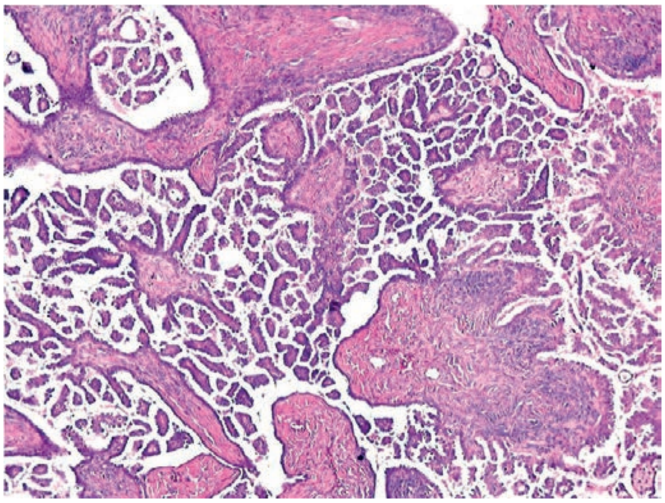

Figure 35.28 Ovarian serous borderline tumor with a micropapillary pattern of growth.

extra-ovarian implants, are associated with an excellent prognosis. Curiously the presence of nodal involvement is not associated with an adverse outcome in patients with serous borderline tumor. Micropapillary architecture is associated with a worse prognosis in patients with serous borderline tumor, but it is not established whether this is independent of the well-known association of micropapillarity with higher stage and a component of invasive low-grade serous carcinoma (either within the ovary or at extra-ovarian sites).[143–146] Micropapillary architecture is defined as nonhierarchical branching of elongate filiform papillae and/or a cribriform architecture, with the latter being considerably less common than the former. The papillae should be at least 5 times as long as wide (Fig. 35.28), and the micropapillary focus must be confluent for at least 5 mm. Kurman and colleagues have suggested that serous borderline tumor with micropapillary features should be diagnosed as noninvasive low-grade serous carcinoma; micropapillarity in a stage Ia tumor is not associated with a different prognosis than in a stage Ia conventional serous borderline tumor,[145] and it is therefore not justified, in our opinion, to introduce a new diagnostic term for these patients (i.e. noninvasive low-grade serous carcinoma), especially when the diagnostic criteria have not been shown to be highly reproducible. The borderline category was introduced in the 1950s to clearly indicate that there is a different natural history for patients with these tumors, compared to those with usual carcinoma, and this rationale is still applicable and constitutes an argument against use of the terminology of "noninvasive low-grade serous carcinoma." As noted previously, micropapillary architecture is more likely to be associated with either higher stage disease (ovarian surface involvement or extra-ovarian implants), or the presence of invasive low-grade serous carcinoma, and recurrence as carcinoma is also more common in these tumors, so when micropapillarity is present it should be documented in the pathology report and a careful search for evidence of higher stage or invasion is warranted, but that is the only action we would currently recommend based on the presence of micropapillary variant of serous borderline tumor.

The prognosis of low-grade serous carcinoma is highly dependent on stage. For stage Ia disease the prognosis is excellent, but in most reported cases there is extra-ovarian spread at the time of diagnosis and these patients have a poor prognosis, similar to that of patients with HGSC.[126,147] With recurrence and tumor progression, low-grade serous carcinomas can become higher grade, with increased mitotic activity. These tumors differ from usual HGSC in lacking *TP53* mutations[124] (i.e. they are not examples of "progression" from low-grade serous carcinoma to HGSC of the usual type).[148]

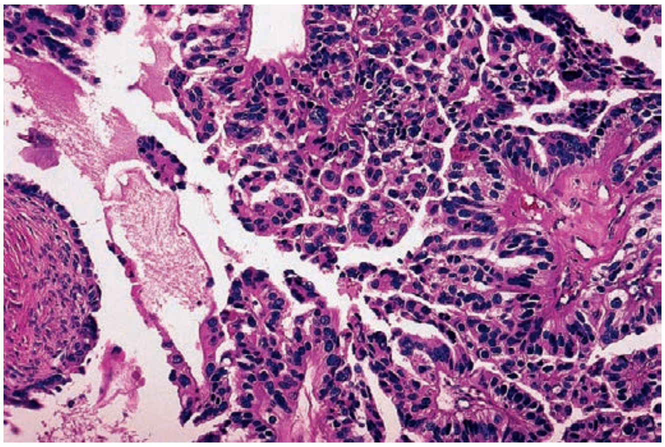

Figure 35.29 High-grade serous carcinoma with papillary architecture.

Immunohistochemistry and Molecular Pathology

Immunohistochemically, the typical keratin profile of low-grade serous tumors is CK7+/CK20−.[149] They also express CK8, 18, and 19, EMA, B72.3,[150–152] vimentin,[153] glial fibrillary acidic protein (GFAP) (occasionally),[152] the β-subunit of human chorionic gonadotropin (hCG) (in a minority of cases),[154] and receptors for estrogen and progesterone.[155,156] A small minority (around 10%) of serous tumors stain for calretinin and/or inhibin, a potentially confusing finding in the differential diagnosis with sex cord–stromal tumors.[157] WT1 and PAX8 stain most low-grade ovarian serous tumors.[158–160] Serous borderline tumors and low-grade serous carcinoma have relatively few mutations and are typically diploid. The most common mutations are in *KRAS* and *BRAF*.[100,123]

High-Grade Serous Carcinoma

Most HGSCs show bilateral ovarian involvement. Tubal fimbrial involvement is often noted on gross examination and is usually unilateral. On sectioning the ovarian masses are solid and cystic, with conspicuous hemorrhage and necrosis. Microscopically, HGSC is characterized by morphologic heterogeneity, and there is often an admixture of different architectural patterns including papillary, micropapillary, slit-like, glandular, microcystic/ microglandular, solid, and transitional-like patterns. While papillary elements and slit-like spaces are characteristic of HGSC (Figs. 35.29 and 35.30), well-formed rounded glands are also common, resulting in a pseudoendometrioid appearance (Fig. 35.31). The tumor cells usually have scant to moderate amounts of cytoplasm, but occasionally there is abundant eosinophilic or clear cytoplasm, or cells with vacuoles and intracytoplasmic mucin, resulting in a signet ring appearance. The neoplastic cells consistently show high-grade nuclear features, with significant pleomorphism and a high mitotic rate with frequent abnormal mitotic figures. As a rule, high-power microscopic fields with multiple mitoses are easily found, and individual bizarre tumor giant cells are also often present, features that are helpful in ruling out low-grade serous carcinoma. Areas of necrosis are common, but psammoma bodies are less frequently encountered than in low-grade serous carcinoma.

Prognosis

When there is a general discussion of "ovarian carcinoma" it is usually concerned with HGSC, as it accounts for 70% of all cases

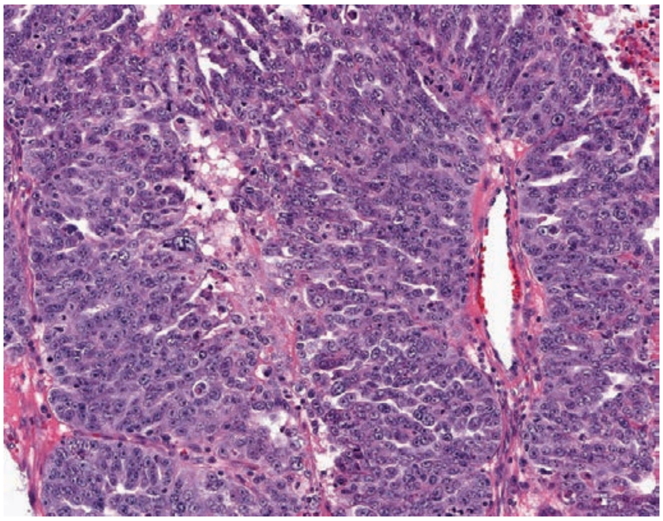

Figure 35.30 High-grade serous carcinoma with slit-like spaces.

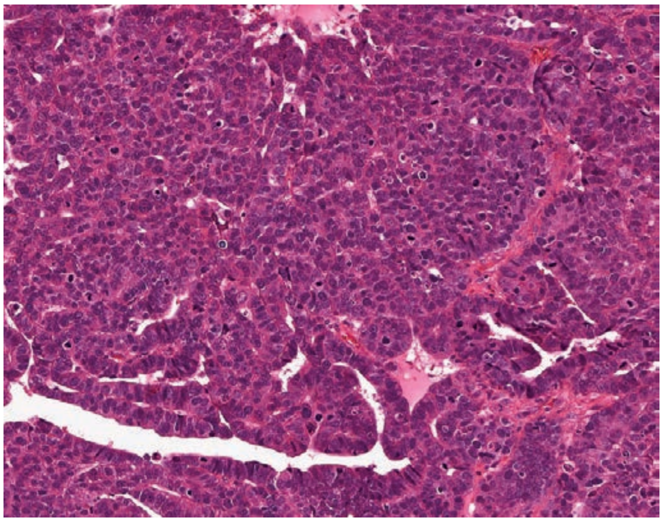

Figure 35.31 **High-Grade Serous Carcinoma With Gland Formation.** This is a common finding in high-grade serous carcinoma and is not evidence of a component of endometrioid carcinoma.

(see Table 35.2) and a disproportionate number of the deaths due to disease. The latter is attributable to these tumors being high-stage at diagnosis, which is itself attributable to most of them originating in the tubal fimbria (discussed later). There has unfortunately been little progress in treatment of HGSC. Although most patients experience a remission, recurrence and death due to progressive disease are usual. Treatments targeting the molecular abnormalities of HGSC, such as PARP inhibitors, show great promise,[161] but they have not yet entered practice as adjuvant treatment, where they would be given with curative intent. Nonetheless, the activity they show against recurrent HGSC is impressive and they will undoubtedly become more widely used over the coming years.

Site of Origin

There is now irrefutable evidence that most extrauterine HGSCs arise from the fallopian tube (most commonly the fimbrial end) from a precursor lesion referred to as serous tubal intraepithelial carcinoma (STIC).[162–167] It was first recognized that the fimbrial end of the fallopian tube is the site of origin of a large majority of HGSCs in patients with a germline BRCA1 or BRCA2 mutations, based on the fimbrial location of early carcinomas identified in risk-reducing salpingo-oophorectomy specimens.[166,168–170] This observation became possible only with more detailed and systematic examination of the fallopian tubes; introduction of the **S**ectioning and **E**xtensively **E**xamining the **FIM**bria (SEE-FIM) protocol[166] resulted in a dramatic increase in the number of STICs and small invasive HGSCs detected. It is now clear that STIC and small tubal mucosal HGSCs are found in sporadic "ovarian" HGSCs at comparable frequency to what is seen in high-risk patients with HBOCS. Adding to the cases with STIC those where the fimbrial end of the tube is overgrown and incorporated into an adnexal mass, one is left with fewer than 20% of HGSCs where there is not tubal involvement. It is also clear that the tubal lesions usually precede the disease in the ovaries and other extratubal sites.[170] Four recent studies have reported on HGSC diagnosed as an incidental finding at surgery carried out for unrelated reasons; these occurred in women who were not at high risk for ovarian cancer.[171–174] The tubal mucosa was involved in 100% (48 of 48) of cases and STIC, with or without an invasive mucosal carcinoma, was identified in 98% (47 of 48).

It should be remembered that fallopian tube mucosal involvement and ovarian involvement by uterine or nongynecological primary tumors can occur and can mimic STIC. Most cases with both endometrial serous carcinoma (either intraepithelial or invasive) and concomitant unilateral or bilateral HGSC in the ovary (and/or STIC or HGSC in the fallopian tube) represent adnexal metastases from an endometrial primary.[161] WT1 may be of value in these cases, as most tubal HGSCs exhibit diffuse nuclear positivity with WT1, while most uterine serous carcinomas are negative. Unfortunately, there is some overlap in that a proportion of uterine serous carcinomas are WT1 positive (the percentage has varied between studies, but may be up to 30%) and a small percentage of tubal HGSCs are WT1 negative.[175]

While the assignment of primary site in HGSC does not change management, it is often a requirement for tumor registries, and a uniform approach to site assignment is desirable. The following guidelines take into account recent advances in our understanding of the histogenesis of HGSC, described previously[176]: A. Primary site should be assigned as tubal in the presence of STIC or invasive mucosal HGSC in either fallopian tube, or when either tube is partly or fully incorporated into and inseparable from a tubo-ovarian mass. B. Primary site should be assigned as ovarian only when there is ovarian involvement and the fallopian tubes are clearly visible, have been dissected away from the surface of the ovaries, fully examined by a standardized SEE-FIM protocol and neither STIC nor invasive mucosal carcinoma is present in either tube. C. Primary site should be assigned as peritoneal only when both tubes and both ovaries are grossly and microscopically normal; primary peritoneal HGSC should only be diagnosed in a specimen from primary surgery (as neoadjuvant chemotherapy can impact on the ability to assign primary site by changing the disease distribution) and only after complete examination of both tubes and both ovaries using a standard protocol.

Differential Diagnosis

The differential diagnosis between HGSC and low-grade serous carcinoma was discussed in the preceding section. The differential diagnosis also includes endometrioid carcinoma, clear cell carcinoma, and undifferentiated carcinoma (Fig. 35.32). As endometrioid-like glandular formation, clear cell change or solid undifferentiated architecture are rarely present throughout a well-sampled tumor, the presence of typical HGSC will establish the diagnosis. In problematic cases (e.g. a small biopsy with limited tissue available to seek different architectural patterns), immunostaining may help (Table 35.4). For a diagnosis of undifferentiated carcinoma, it should be undifferentiated throughout; by definition, even a minor component showing differentiation excludes a diagnosis of undifferentiated carcinoma. Similarly, one should resist the urge to diagnose mixed HGSC and endometrioid carcinoma, or HGSC and clear cell carcinoma. True admixtures of these components are rare, and most purported examples are, based on clinical and immunohistochemical features, HGSC with glandular architecture, or clear cells, respectively.[177,178]

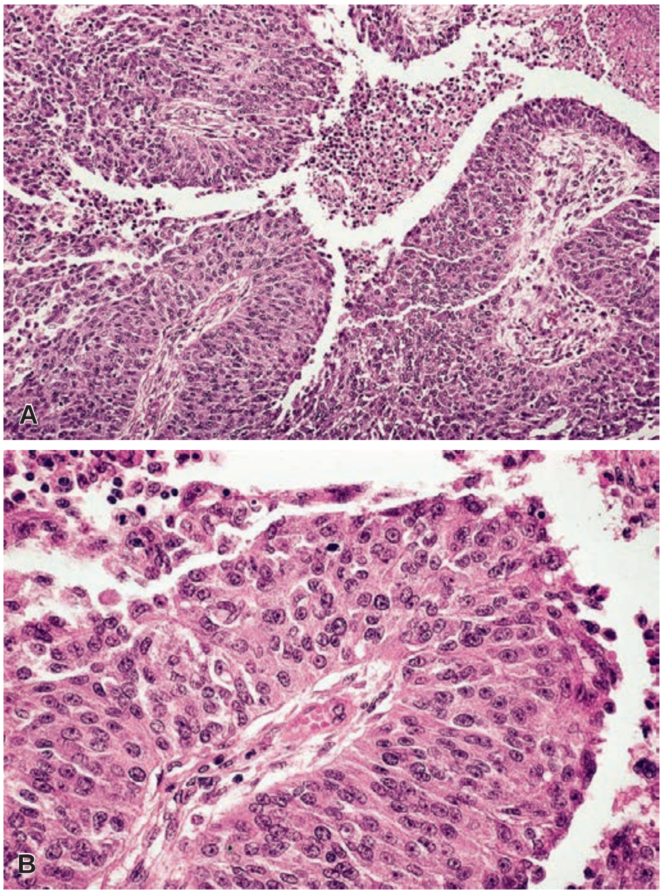

Figure 35.32 **A** and **B,** High-grade serous carcinoma with solid and transitional-like architecture.

Immunohistochemistry and Molecular Morphology

The immunoprofile of HGSC, compared to other ovarian carcinomas, is show in Table 35.4. With regard to the differential diagnosis with mesothelioma, MOC31, Ber-EP4, PAX8, and hormone receptors are more likely to be expressed by serous carcinoma, whereas calretinin, thrombomodulin, and CK5/6 are more likely to be seen in mesothelioma.[179–182] The Cancer Genome Atlas (TCGA) study, with sequencing of more than 300 tubo-ovarian HGSCs,[183] confirmed the ubiquity of *TP53* mutations and also highlighted the fact that apart from *TP53*, *BRCA1*, and *BRCA2*, there are few *recurrent* mutations in HGSC, in contrast to many other tumor types. It is, instead, characterized by aneuploidy and large numbers of somatic copy number alterations, rather than recurrent mutations. The mechanism accounting for this phenotype is the presence of defects in cellular mechanisms that allow for high-fidelity repair of DNA double strand breaks, which leads to mutation-prone repair mechanisms and resultant aneuploidy/copy number abnormalities. Genetic abnormalities accrue rapidly within the dividing tumor cells, leading to dramatic intratumoral heterogeneity at both the genetic and morphologic level. In a study of advanced-stage HGSC where tumor from multiple anatomic sites in the same patient was compared, fewer than 50% of mutations were present in all sampled specimens.[184] Thus, loss of the ability to repair DNA double strand breaks is as an early event in HGSC, followed by accrual of large numbers of copy number abnormalities that result in striking inter- and intra-tumoral heterogeneity. A minority of HGSCs have amplification of cyclin E1 (CCNE1), a molecular abnormality that is mutually exclusive of BRCA mutation and is associated with a worse prognosis/platinum resistance, compared to HGSCs without CCNE amplification.[185–187] CCNE amplification often coexists with AKT amplification, and treatment directed against cyclin-dependent kinase-2 (CDK2) and AKT, with small molecule kinase inhibitors, is a potential approach to targeted treatment of these platinum resistant HGSCs.[188]

Mucinous Tumors

Mucinous neoplasms are less common than serous neoplasms and are bilateral in less than 10% of cases.[189] As with their serous counterparts, ovarian mucinous tumors have been divided into *benign* **(mucinous cystadenoma)**, *borderline*, and *malignant* **(mucinous carcinoma);** most mucinous tumors are benign or borderline. Grossly, they tend to grow larger than the serous types and are partially or completely cystic, often multiloculated and have a smooth surface. A fluid to viscous material of mucoid nature is present in the lumen (Figs. 35.33–35.35).

Table 35.4 Markers of value in histotype diagnosis of ovarian carcinoma

	HGSC	LGSC	ENDOMETRIOID	CLEAR CELL	MUCINOUS
WT1	Diffuse positive	Diffuse positive	Negative	Negative	Negative
p53	Mutation type	Wild type	Wild type or mutation type	Wild type	Wild type or mutation type
p16	Diffuse positive	Focal positive	Focal positive	Variable	Variable
ER	Diffuse or focal positive or negative	Diffuse positive	Diffuse positive	Negative	Negative or focal positive
HNF-1β	Negative	Negative	Negative	Diffuse or focal positive	Variable
Napsin A	Negative	Negative	Negative	Diffuse or focal positive	Negative

From Singh N, McCluggage WG, Gilks CB. High-grade serous carcinoma of tubo-ovarian origin: recent developments. *Histopathology*. 2017 May 6. [Epub ahead of print]

Note: These are the most common staining patterns, but exceptions may occur with all of the markers.

ER, Estrogen receptor; *HGSC*, high-grade serous carcinoma; *HNF-1β*, hepatocyte nuclear factor-1β; *LGSC*, low-grade serous carcinoma

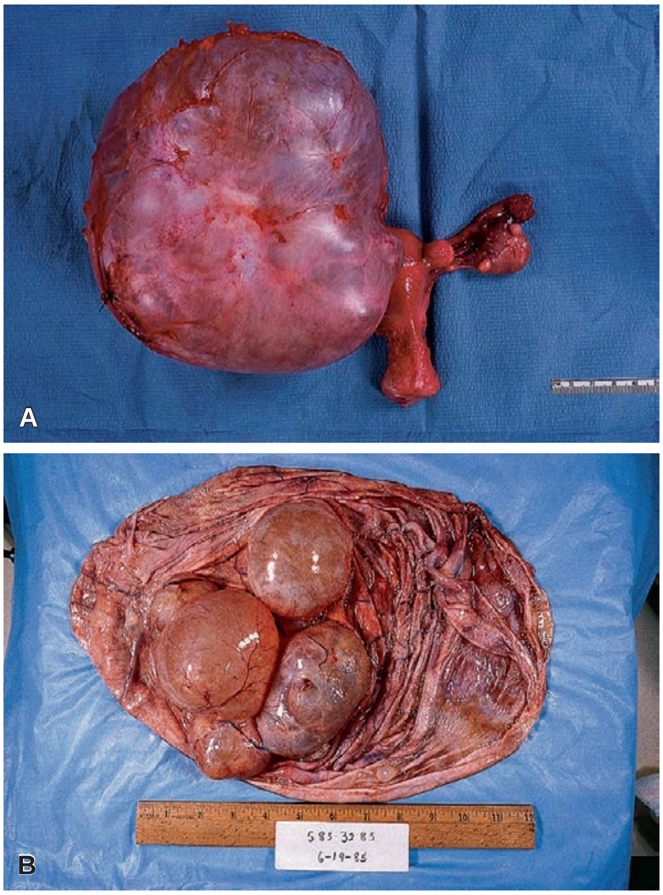

Figure 35.33 **A** and **B,** Outer and inner aspect of mucinous cystadenoma.

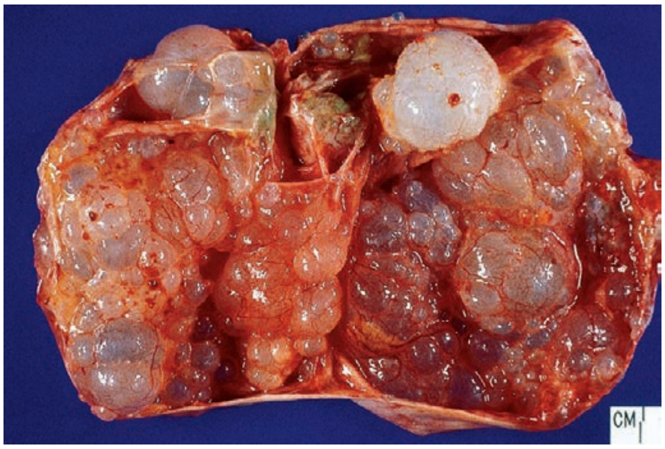

Figure 35.34 Gross appearance of a mucinous ovarian neoplasm that had borderline features at the microscopic level.

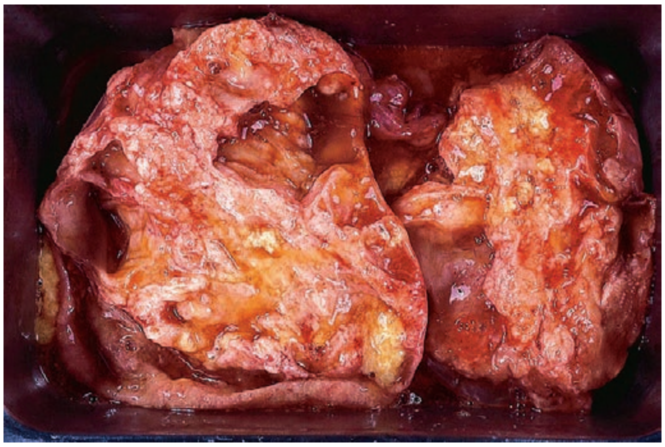

Figure 35.35 **Gross Appearance of Mucinous Cystadenocarcinoma.** The neoplasm is predominantly solid, but some mucin-containing cystic spaces can still be appreciated.

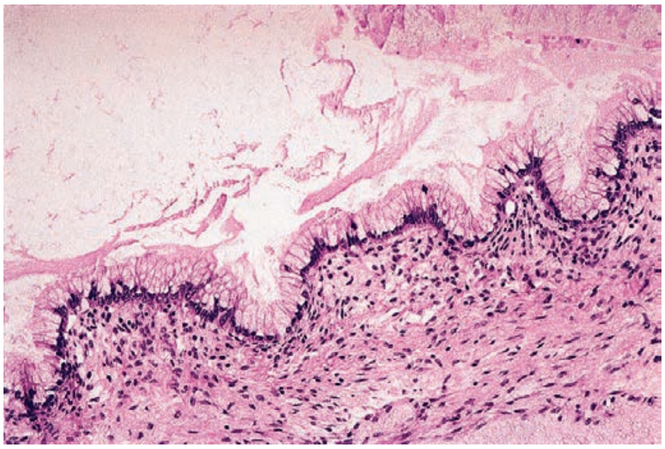

Figure 35.36 **Lining of Mucinous Cystadenoma.** Goblet cells are evident.

The epithelium is referred to as *intestinal* (in contrast to the endocervical-like epithelium of seromucinous tumors, described in the next section) and is characterized by an epithelial lining with a “picket fence” appearance, goblet cells, Paneth cells, endocrine cells, the secretion of gastrointestinal or pancreatobiliary type mucin,[190] and the production of intestinal enzymes such as lipase, trypsin, amylase, and sucrase (Fig. 35.36).[191] The endocrine cells, which are more common in the borderline category, are argyrophil and sometimes argentaffin.[192] 5-Hydroxytryptamine (serotonin, 5-HT), ACTH, gastrin, somatostatin, and other peptide hormones have been detected in this endocrine cell population by immunohistochemistry.[193–196] There is usually no clinical evidence of hormone excess, but cases associated with Zollinger–Ellison syndrome have been described.[197] Exceptionally, there is a focal component of signet ring cells, which may lead to a mistaken diagnosis of Krukenberg tumor,[198] but it should be noted that the presence of signet ring cells usually is an indication that you are dealing with a metastasis to the ovary.[199]

Occasionally, mucinous tumors of intestinal type are found in association with a teratoma or carcinoid tumor in the same ovary.[200] These uncommon mucinous neoplasms associated with teratomatous elements are of germ cell origin, based on the frequent finding of homozygosity, with genotypic concordance between the mucinous neoplasm and the teratoma.[201,202] Those mucinous tumors lacking a teratomatous component have a normal heterozygous genotype, indicating that they are most probably of somatic cell origin. The mucinous tumors of germ cell origin are more likely to be associated with mucin dissection through the ovarian stroma (pseudomyxoma ovarii). Importantly, the mucinous tumors of germ cell origin, which can be benign, borderline, or malignant, have a fully intestinal immunophenotype (i.e. CK20+, CK7−, unlike the mixed intestinal/müllerian immunophenotype typical of mucinous tumors without a teratomatous component [CK20 and CK7+]).

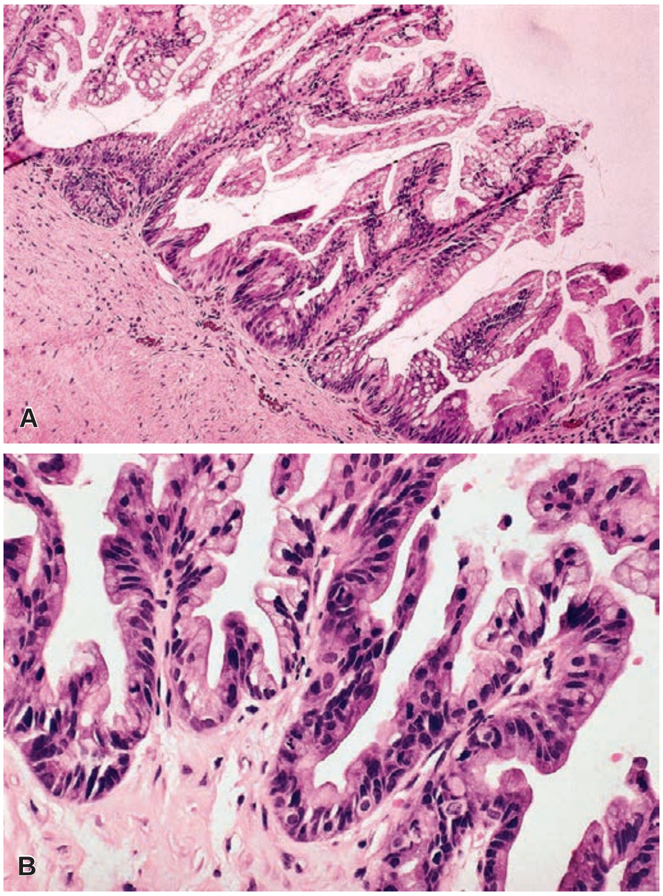

Figure 35.37 **A** and **B,** Mucinous borderline tumor of intestinal type, with focal intraepithelial carcinoma.

The distinction between benign and borderline mucinous tumor is based on the presence of cytologic atypia and stratification in the latter (Fig. 35.37), which is absent in the former. It is easy to understand how this distinction can be highly subjective. If borderline change is focal, occupying less than 10% of the cyst lining, which is otherwise benign, the designation of mucinous cystadenoma with focal atypia or focal proliferation has been suggested, and all such tumors have been benign on follow-up.[203] Almost all mucinous borderline tumors of intestinal type have been associated with a benign clinical course, but very rare exceptions have been reported.[204] The distinction between mucinous borderline tumor and carcinoma is based on the presence of invasion, and two patterns of invasion are recognized in mucinous tumors. The most common is expansile pattern, in which there is marked complexity of the glandular architecture. There is minimal or no intervening stroma between the glands, which show cribriform or labyrinthine patterns (Fig. 35.38). The contours of the gland margins are smooth, unlike what is seen with infiltrative or destructive pattern of invasion. The architecturally complex glands are invariably lined by atypical cells, showing increased layering and papillae (e.g. budding, bridging, and/or appearance of solid foci; see Fig. 35.38).[199,205] Infiltrative pattern of invasion (also referred to as "destructive invasion") is recognized by the presence of single cells or irregular cell clusters in stroma that may show desmoplasia. This pattern of invasion is less common and may be associated with a worse prognosis than purely expansile pattern of invasion; however, it should be noted that tumors with only expansile pattern of invasion are fully malignant and may metastatsize.[199,205]

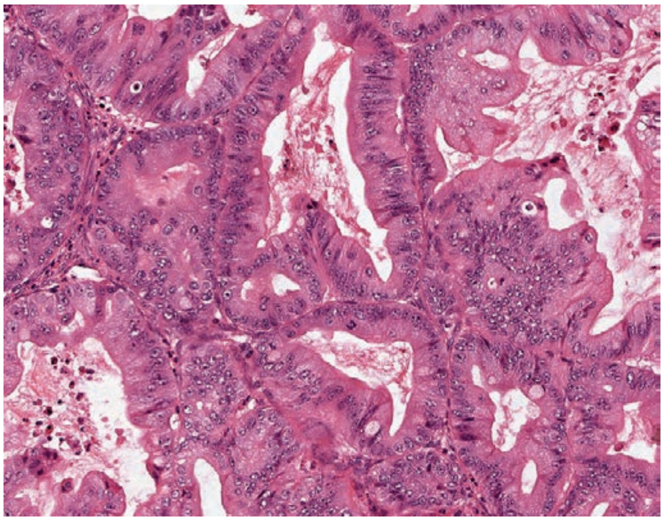

Figure 35.38 Mucinous carcinoma with expansile pattern of invasion; there is minimal stroma between the closely packed glands.

Within the borderline category we also recognize mucinous borderline tumor with focal intraepithelial carcinoma (see Fig. 35.37B).[199] The degree of cytologic atypia is greater than what is encountered in a usual mucinous borderline tumor; it is analogous to adenomatous polyps of the colon with high-grade dysplasia, featuring malignant-appearing epithelial cells showing increased stratification and sometimes cribriform architecture. Clinically, the outcome for patients with mucinous borderline tumor with intraepithelial carcinoma is usually favorable, but occasional patients have experienced a fatal recurrence.[199,206] Mucinous borderline tumors with microinvasion (<5 mm) should be distinguished from frankly invasive (≥5 mm) carcinoma; microinvasion is usually associated with an excellent prognosis.[199,207,208]

There is a subgroup of mucinous tumors in which the stromal component is particularly prominent. These have been designated *mucinous adenofibroma* or *cystadenofibroma* if benign and *mucinous adenocarcinofibroma* and *cystadenocarcinofibroma* if malignant. The benign ones are sometimes misinterpreted as malignant and even as metastatic because of the irregularly shaped glands in a "desmoplastic" stroma,[209] or as microinvasive because of the presence of micronests of cells.[210]

Exceptionally, ovarian mucinous tumors have been found to contain foci of: (1) *sarcoma-like nodules*, with a configuration and cytologic composition similar to those of giant cell tumor of soft parts,[211] characterized by a lack of reactivity for keratin[212]; (2) *sarcoma*, usually spindle shaped, sometimes with heterologous features,[213,214] and also unreactive for keratin; and (3) *anaplastic carcinoma*, with pleomorphic round to spindle cells that are immunoreactive for keratin.[215,216] The distinction between the latter two lesions is very tenuous, both on microscopic and histogenetic grounds (as it is in the pancreas or thyroid under similar circumstances), and both are associated with a poor prognosis unless they present as stage I lesions.[217] Actually, we favor the interpretation that the sarcoma-like nodules themselves are not a reactive phenomenon,[218] but rather are of neoplastic nature and related histogenetically to the other two processes, a possibility also expressed by others[219] and supported by the occasional overlap and coexistence of these various lesions.[217] However, it is important to consider the sarcoma-like nodules separately because of their better prognosis.[211,216,218,220] On occasion, the appearance of the mural nodule is that of a benign leiomyomatous growth.[221]

Immunohistochemically, the tumor cells of ovarian mucinous tumors express CEA (more so the intestinal types and/or malignant tumors),[222] keratin, EMA (particularly if malignant),[223] MUC5AC (a gastrin mucin gene), DPC4 (a nuclear transcription factor inactivated in about half of pancreatic adenocarcinomas),[224] hepatocyte nuclear factor 1,[225] and hepatocyte nuclear factor 4 alpha.[226] Importantly, the tumor cells express markers of gastrointestinal type differentiation such as CK20, SATB2 (very rarely), and CDX2,[224,227–230] as well as CK7, which is more strongly expressed than the intestinal markers in most cases.[230] As noted previously, mucinous tumors of germ cell origin have a more purely intestinal immunophenotype (strong diffuse CK20, SATB2 and CDX2, with negative CK7). In contrast to other types of ovarian epithelial tumor, PAX8 is often negative, as are WT1 and ER.[161]

Only rarely is a mucinous tumor arising from the ovary accompanied by extensive deposits of intra-abdominal mucin (pseudomyxoma peritonei); a large majority of these tumors are metastatic to the ovary and peritoneal cavity from an appendiceal origin, and are, therefore, discussed in Chapter 16.

The chief differential diagnosis is with metastatic carcinoma. A simple algorithmic approach has been advocated for the distinction between primary and metastatic mucinous tumors of the ovary, relying in size and laterality. Tumors that are unilateral, smooth surfaced and more than 13 cm, without mucinous ascites, are highly likely to be primary ovarian mucinous neoplasms.[231] The differential diagnosis also includes high-grade serous or endometrioid carcinoma, especially in those mucinous carcinomas where there is loss of intracellular mucin with increasing grade. The presence of a lower grade or borderline area can support the diagnosis of mucinous carcinoma, as can the absence of WT1 immunoreactivity and negative (or only focally positive) immunostaining for ER (see Table 35.4).

Seromucinous Tumors

Formerly considered a variant of mucinous tumor, the seromucinous neoplasms have been recognized as a distinct tumor type in the 2014 WHO classification. They differ from mucinous tumors of intestinal type morphologically and clinically, and such a distinction is therefore justified. They have also been referred to as *endocervical*, *endocervical-like,* or *müllerian*, and are characterized by a papillary architecture similar to that of serous tumor but with a lining of tall nonciliated cells with basally located nuclei and abundant intracellular mucin (Fig. 35.39). The stroma of the papillae is typically edematous and infiltrated by neutrophils. Seromucinous tumors express müllerian-type markers (such as hormone receptors, CA 125, and mesothelin) and resemble endocervical epithelium both at the light and electron microscopic level.[232] It has been pointed out that the seromucinous tumors share more morphologic and immunohistochemical features with the endometrioid or serous (or even clear cell) carcinomas than they do with mucinous tumors of intestinal type.[233–235] Seromucinous borderline tumors frequently have *ARID1A* mutation and show loss of ARID1A protein expression, at a frequency similar to that of endometrioid tumors.[236] In addition to the mucinous component, there are often admixed serous and, occasionally, squamous or clear cell components, leading to a proposal that a more apt designation for the seromucinous group of neoplasms would be "mixed müllerian" tumors. Having only just set these tumors apart as a separate entity in the 2014 WHO classification, it is difficult to muster enthusiasm for a name change so soon.

Most seromucinous tumors are benign or borderline, and only a handful of carcinomas have been reported. The borderline tumors are associated with a favorable prognosis, even when extra-ovarian implants are present.

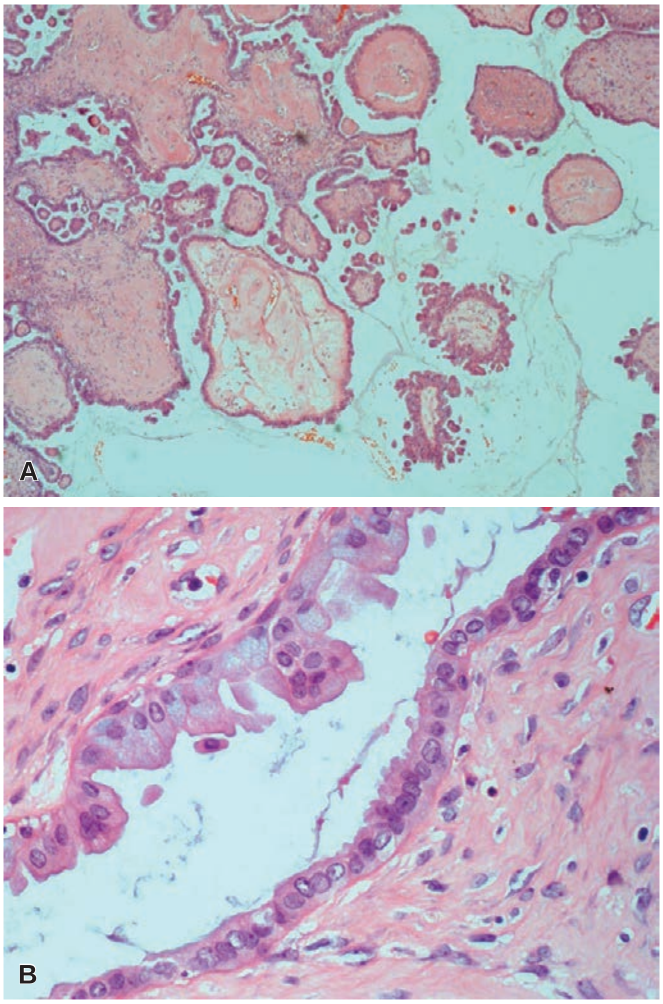

Figure 35.39 Seromucinous Borderline Tumor. At lower magnification **(A)** it resembles serous borderline tumor, but with prominent edema of the stroma in papillae. At higher magnification there is prominent intracellular mucin in some of the cells **(B)**.

The differential diagnosis for a benign seromucinous tumor includes a benign mucinous tumor of intestinal type. In practice, it is not clinically relevant to subtype a benign mucinous tumor, and a diagnosis of "mucinous cystadenoma" (or adenofibroma), without further qualification, can be made based on H&E as it would be an inappropriate use of resources to apply special stains in this setting. The seromucinous borderline tumors are sufficiently distinctive such that there is usually no doubt about the diagnosis on routine H&E stains alone. The presence of conspicuous intracellular mucin sets them apart from serous borderline tumor, the tumor they most resemble. Although seromucinous carcinoma has been reported, it is not entirely clear how they differ from the more commonly diagnosed endometrioid carcinoma with mucinous differentiation.

Endometrioid Tumors

Endometrioid carcinoma comprises 10% of all primary ovarian carcinomas (see Table 35.3). Coexistent endometriosis can often be demonstrated,[237] and some of the tumors can be seen arising from these endometriotic foci. However, the identification of endometriosis is not a prerequisite for the diagnosis of endometrioid carcinoma.

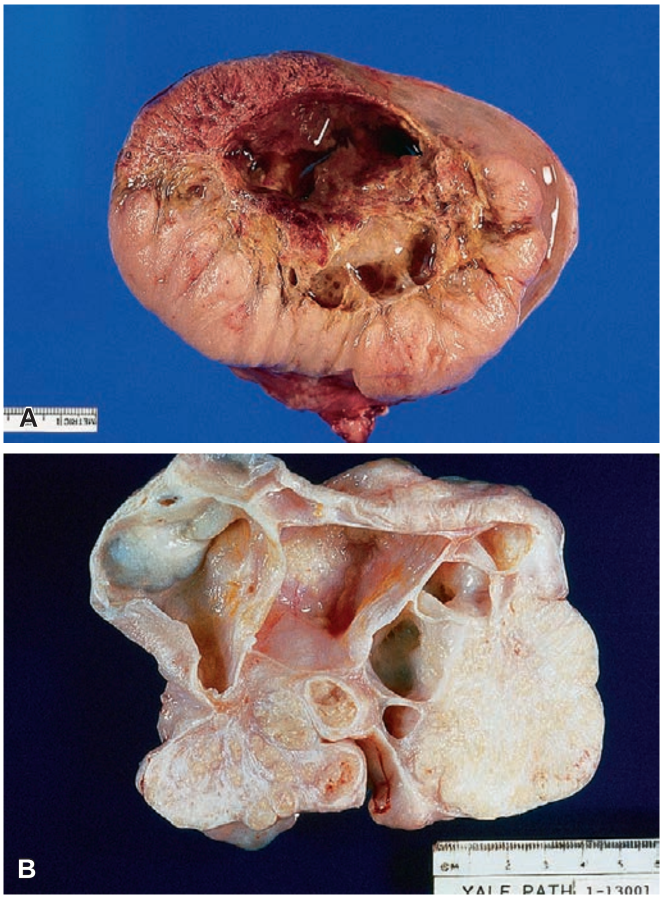

Figure 35.40 **A** and **B,** Gross appearances of ovarian endometrioid carcinoma. Both tumors show a combination of solid and cystic appearances.

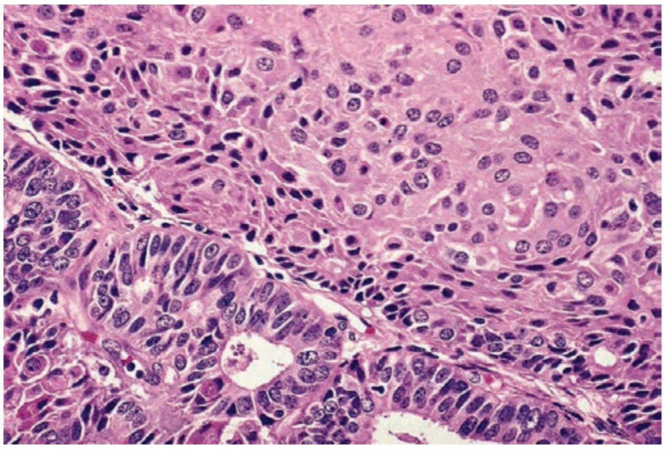

Figure 35.41 Well-differentiated endometrioid ovarian carcinoma with extensive squamous differentiation.

Grossly, endometrioid carcinoma may present as a cystic or solid mass (Fig. 35.40). The content tends to be hemorrhagic rather than serous or mucinous. Visible papillary formations are usually absent or inconspicuous. Microscopically, the tumors strongly resemble the appearance of the ordinary type of endometrial adenocarcinoma—hence their name (Fig. 35.41).[238,239] Most are well differentiated (grade 1 or 2, according to the FIGO grading system used for endometrial carcinomas of endometrioid type), with or without papillary formations. Half of the tumors have foci of squamous metaplasia (see Fig. 35.43).[240] Morules may express CDX2 and β-catenin (nuclear translocation).[241] In contrast to serous tumors, psammoma bodies are exceptional. Approximately 10% of endometrioid carcinomas have a component of non-neoplastic luteinized stromal cells.

The keratin produced by these ovarian neoplasms can result in the formation of peritoneal keratin granulomas.[74] It seems likely that at least some of the reported cases of primary **squamous cell carcinomas** of the ovary represent the extreme expression of this metaplastic tendency of endometrioid carcinoma.[242–245] Parenthetically, the other large category of ovarian squamous cell carcinoma is that associated with benign cystic teratomas (i.e. secondary somatic transformation).[246]

Histochemically, mucin may be found within the glandular lumina and in the apical border of the tumor cells. Some tumors show mucinous metaplasia, just as can be seen in endometrioid carcinomas of the endometrium; these tumors lack goblet cells and strongly express ER, which serves to distinguish them from mucinous tumors of intestinal type (see Table 35.4). Scattered argyrophil cells are seen in almost half of cases.[247]

Immunohistochemically, the tumor cells are positive for keratin, EMA, vimentin, and PAX8, whereas CEA is usually negative or weak.[248] There can also be positivity for CA 19-9 and hPL.[249,250]

Mutations leading to β-catenin deregulation are found in nearly half of ovarian endometrioid adenocarcinomas.[251] Many endometrioid and clear cell carcinomas (i.e. ovarian tumors related to endometriosis) have mutations of *ARID1A*, a tumor suppressor gene, in stark contrast with serous carcinomas, which do not have this mutation.[98]

In some endometrioid carcinomas, the neoplastic glands are small and tubular or solid and elongated, simulating the pattern of sex cord–stromal tumors, particularly of Sertoli–Leydig cell type.[252,253] These are referred to as endometrioid carcinoma resembling sex cord–stromal tumors.[254] Features that favor a diagnosis of endometrioid carcinoma in such cases are the older age of the patients, the usual absence of endocrine manifestations, and the occurrence elsewhere in the tumor of larger tubular glands, foci of squamous metaplasia, luminal mucin accumulation, adenofibromatous components, immunoreactivity for keratin (including CK7) and EMA, and negativity for inhibin.[255,256] Other endometrioid carcinomas simulate the appearance of granulosa cell tumors, from which they can be distinguished on immunohistochemical grounds.[257]

Other morphologic variations of endometrioid carcinoma include presence of yolk sac elements,[258,259] tumors composed of ciliated cells,[260] tumors composed of oxyphilic (oncocytic) epithelium,[261,262] and tumors containing foci of collagenous spherulosis that simulate squamous metaplasia.[263] Endometrioid carcinomas containing foci of hepatoid differentiation have also been described.[264] Just as for endometrial endometrioid tumors, there can be de-differentiation with emergence of undifferentiated carcinoma from a low-grade endometrioid tumor.[265] This is associated with loss of expression of one or more proteins of the SWI/SNF chromatin remodeling complex (BRG1, INI1, ARID1A, ARID1B) and mutation of the corresponding gene(s) in most cases.[266]

Benign and borderline types of endometrioid ovarian tumors exist, in addition to the malignant ones.[261,267–269] Most of the benign endometrioid tumors, which are rare, have a prominent stromal component and have been designated as adenofibromas or cystadenofibromas, depending on the degree of cystic change (Fig. 35.42). Sometimes, benign and malignant areas coexist in the same case.[270,271] In the borderline category, the epithelial changes are equivalent in all respects to those of atypical endometrial hyperplasia (Fig. 35.43). The distinction between borderline endometrioid tumor and low-grade endometrial carcinoma is made based on the same criteria

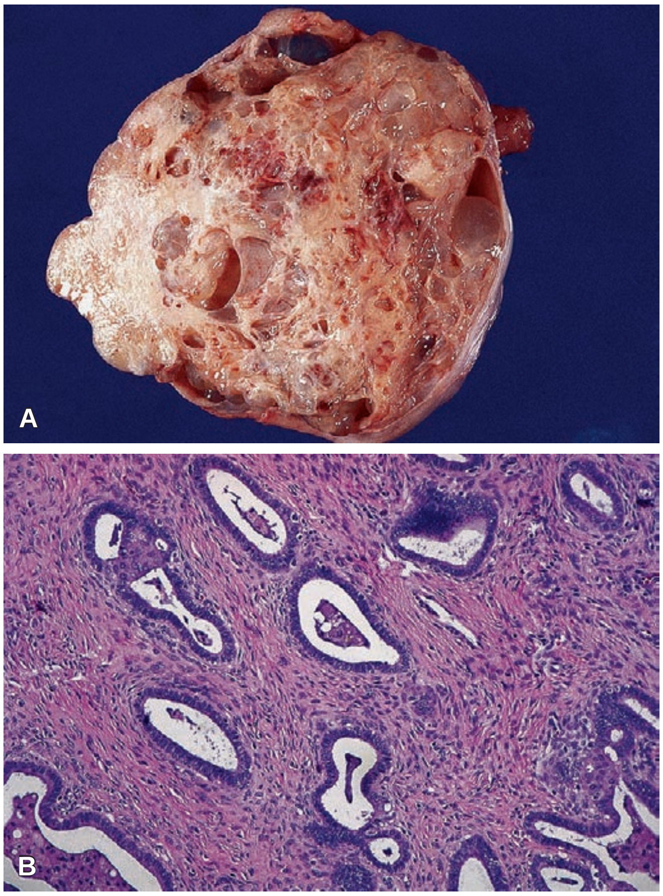

Figure 35.42 **A** and **B**, Gross and microscopic appearance of endometrioid adenofibroma.

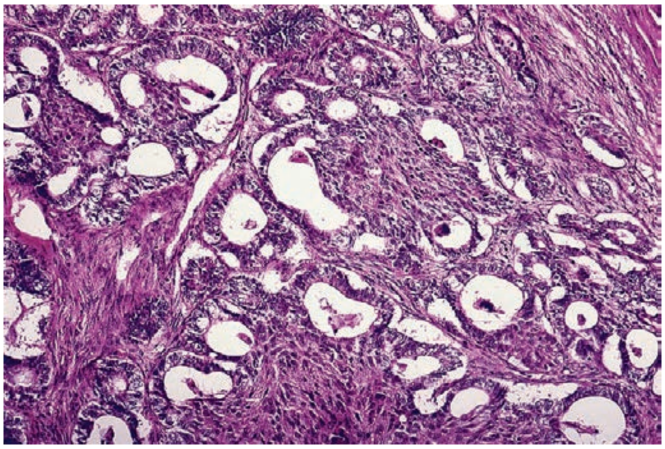

Figure 35.43 Ovarian endometrioid borderline tumor, with glandular architectural complexity.

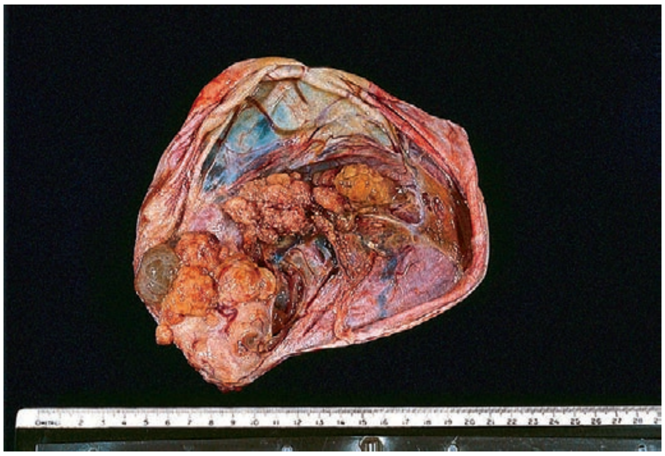

Figure 35.44 **Gross Appearance of Clear Cell Carcinoma of Ovary.** The tumor is predominantly cystic, but it contains several mural nodules.

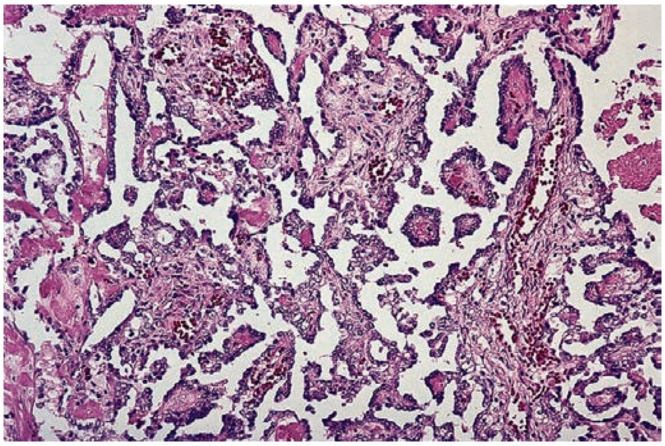

Figure 35.45 A highly papillary configuration is seen in this low-power view of ovarian clear cell carcinoma.

(i.e. primarily based on architectural complexity, but with the additional requirement of associated cytological atypia) as are used in the uterus.

Some patients with endometrioid carcinoma of the ovary have either endometrial hyperplasia or a synchronous endometrial adenocarcinoma, which is often well differentiated and superficial.[272] There is a wide disparity in the reported incidence of the latter occurrence (largely because of different diagnostic criteria used for diagnosis of endometrioid carcinoma in the past), with most series ranging from 15% to 45%. This incidence is higher in recent years due to more accurate diagnosis of endometrioid histotype in the ovary (i.e. there are fewer HGSCs misdiagnosed as endometrioid).[239,272,119] It is frequent enough, in our opinion, that if an endometrial biopsy has not been done previously, it would be warranted to obtain one in any patient with an ovarian endometrioid carcinoma.

The differential diagnosis of endometrioid carcinoma includes serous carcinoma (WT1 positive), mucinous carcinoma of intestinal type (negative or only weakly ER positive), and, in rare instances, sex cord–stromal tumors (negative for EMA and positive for inhibin).

Clear Cell Tumors

Clear cell carcinoma accounts for 10% of ovarian carcinomas (see Table 35.2) and is a distinctive ovarian tumor with a grossly spongy, often cystic appearance (Fig. 35.44), which microscopically can grow in tubulo–cystic, papillary, and solid-sheet patterns (Fig. 35.45).[273,274] Stroma-rich variants of clear cell carcinoma, with a prominent adenofibromatous component, are also common. In contrast to serous carcinomas, the papillae of clear cell carcinoma have a nonhierarchically branched pattern and lack epithelial stratification.[275]

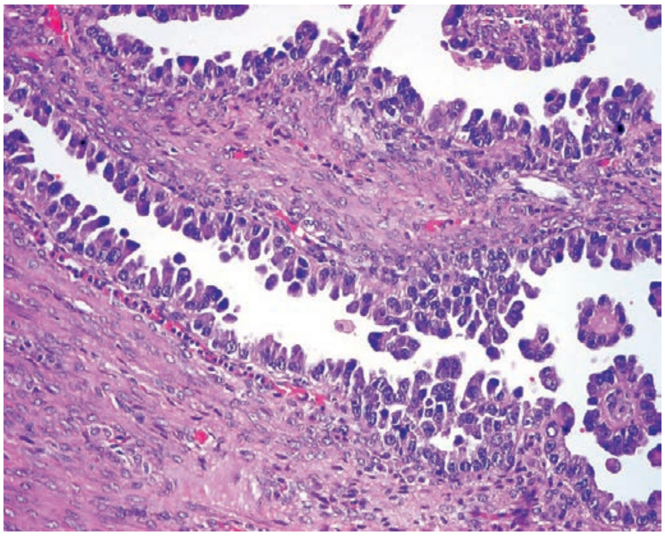

Figure 35.46 **Clear Cell Carcinoma of Ovary.** Note the high nuclear grade and the hobnail configuration.

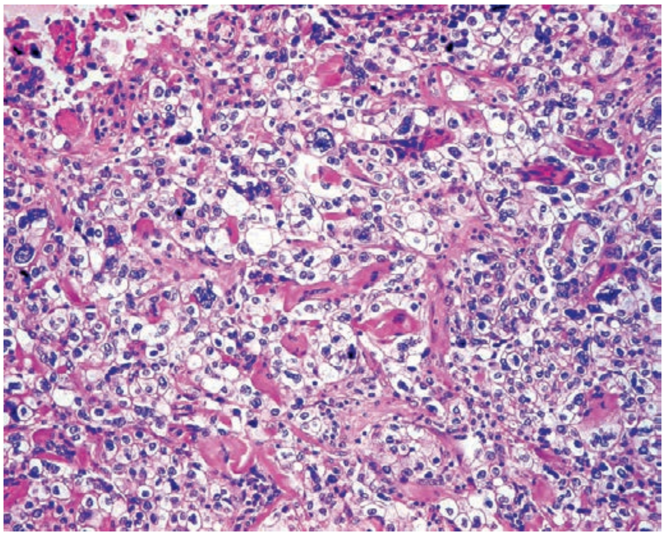

Figure 35.48 Clear cell carcinoma of ovary showing short papillae with hyalinized cores lined by highly atypical cells.

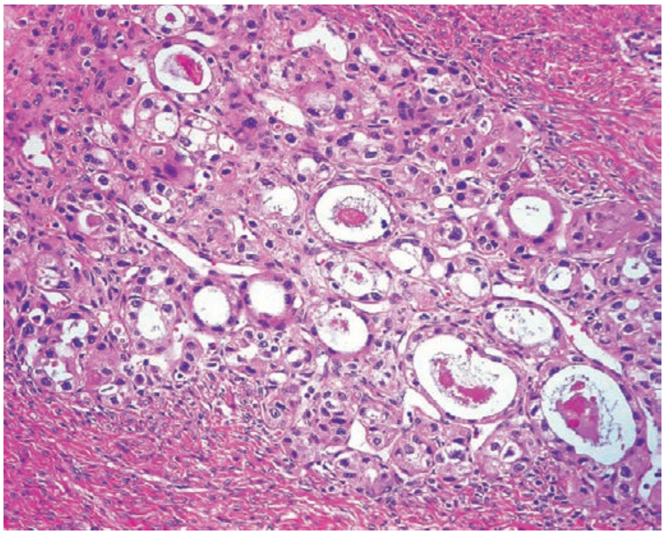

Figure 35.47 Oxyphilic variant of clear cell carcinoma.

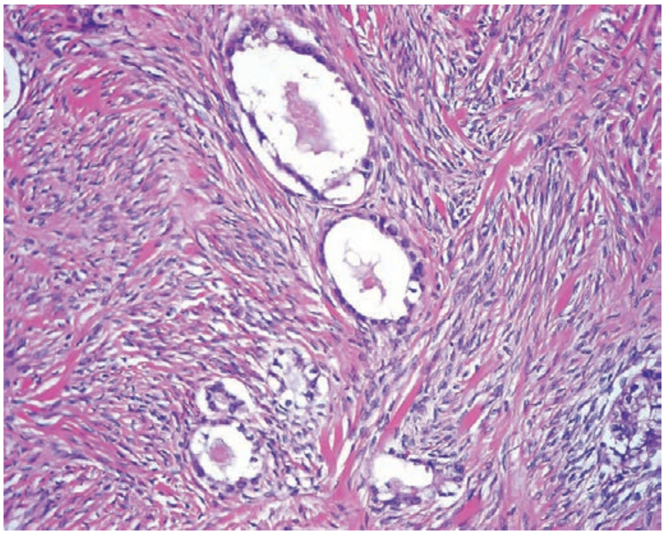

Figure 35.49 Clear cell borderline tumor; the epithelial cells of this adenofibroma show mild to moderate nuclear atypia.

The tumor cells are large and some of the nuclei protrude into the lumina, resulting in a "hobnail" configuration (Fig. 35.46). Their cytoplasm is clear; it often contains glycogen, mucin, and fat, and it may exhibit periodic acid–Schiff (PAS)-positive, diastase-resistant hyaline globules, which are negative for alpha-fetoprotein. In some of the tumor cells, the cytoplasm may appear oxyphilic rather than clear (Fig. 35.47).[268,276] Stromal hyalinization is a common and distinctive feature of clear cell carcinoma, with the stroma of papillae distended by basement membrane material (Fig. 35.48). Immunohistochemically, the tumor cells are always reactive for keratin (CK7, CK5/6, CAM 5.2, 34βE12), EMA, CD15 (Leu-M1), Ber-EP4, vimentin, and PAX8. ER and PR are usually negative or, at most, only focally positive, while p53 shows wild-type staining. Napsin A and hepatocyte nuclear factor-1β (HNF-1β, a transcription factor involved with liver differentiation), are usually expressed.[249,277]

Clear cell carcinoma is frequently associated with pelvic endometriosis, arising in some cases from endometriotic cysts.[278,279] The lining cells of endometriotic cysts may show marked cytological atypia, a finding designated "atypical endometriosis," which is thought to be the precursor of clear cell carcinoma.[98] At the electron microscopic level, the cytoplasmic clearing is seen to be largely due to the accumulation of glycogen.[280]

Benign and **borderline** ovarian clear cell tumors are rare. They can be "pure" or be associated with obviously malignant clear cell carcinomas.[281] Their growth pattern is most commonly that of an adenofibroma.[248] The borderline tumors are identified because of moderate to marked degrees of epithelial proliferation and atypia in the absence of recognizable stromal invasion (Fig. 35.49).[282]

The differential diagnosis of ovarian clear cell carcinoma includes:

- *Metastatic renal cell carcinoma*, which is negative for keratin 34βE12 and positive for CD10, whereas primary clear cell ovarian carcinoma usually (but not always) shows the opposite results.[283]
- *Ovarian yolk sac tumor*, which is characteristically positive for SALL4.[284] It is also positive for glypican-3,[285] but this is also true for about 40% of clear cell carcinomas.[286]

- *Ovarian serous carcinoma*, as a result of the fact that clear cell carcinomas can have a highly papillary pattern of growth,[287] and that serous carcinomas can contain clear cells.[178] An immunohistochemical panel consisting of WT1, estrogen receptor, and HNF-1β is useful in making the distinction.[288]

Brenner Tumor

Brenner tumors constitute between 1% and 2% of all ovarian neoplasms.[289] The average age at presentation is approximately 50 years, about 70% of the patients being over 40 years of age. Some cases are accompanied by signs of hyperestrinism, such as uterine bleeding from endometrial hyperplasia in a postmenopausal woman. The rate of growth is slow, and ascites is rare. Grossly, these tumors vary greatly in size; they are usually unilateral, firm, and white or yellowish white (Fig. 35.50). They closely resemble fibromas or thecomas, except for the frequent presence of small cystic areas filled with opaque, viscous, yellowish-brown fluid. Microscopically, they consist of solid and cystic nests of epithelial cells resembling transitional epithelium (urothelium) surrounded by an abundant stromal component of dense, fibroblastic nature (Fig. 35.51). The epithelial cells have sharply defined outlines; those lining the cysts may be flattened, cuboidal, or columnar. The nuclei of the tumor cells are oval, with a small but distinct nucleolus and longitudinal grooves similar to those seen in granulosa cell tumors (Fig. 35.52). The cytoplasm is clear and immunoreactive for keratin, EMA, and CEA (the latter also present in the lumen of the cysts); nuclear GATA3 reactivity is also common.[290] Scattered argyrophilic cells are present in about one-third of cases; they are positive for chromogranin and 5-HT, have dense-core granules at the ultrastructural level, and are similar to those seen in normal urothelium.[250,291] Steroidogenic enzymes as detected immunohistochemically are usually absent.[292]

Sometimes the cystic formations within the tumor are unduly prominent and accompanied by florid mucinous change.[293] If there is architectural complexity (crowding, stratification of the epithelium) and nuclear atypia but no evidence of invasion, a diagnosis of borderline Brenner tumor is indicated; all such tumors have followed a benign course (Figs. 35.53 and 35.54). *Malignant Brenner tumors* are rare. Some of these have been bilateral.[294,295] They are recognized through the association of the malignant epithelial component with

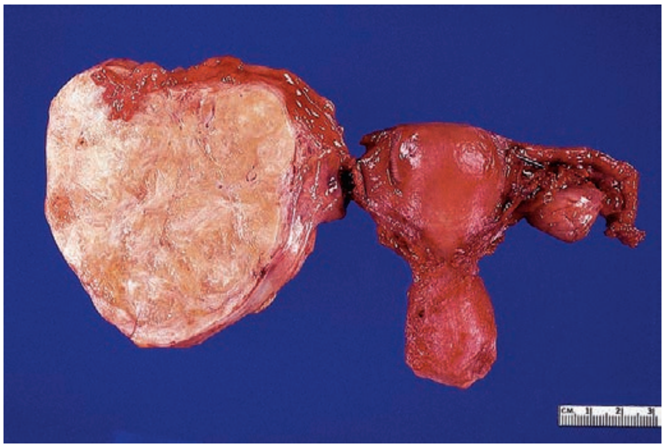

Figure 35.50 Large Brenner Tumor Involving the Right Ovary. The gross appearance of this neoplasm is very similar to that of fibroma or thecoma.

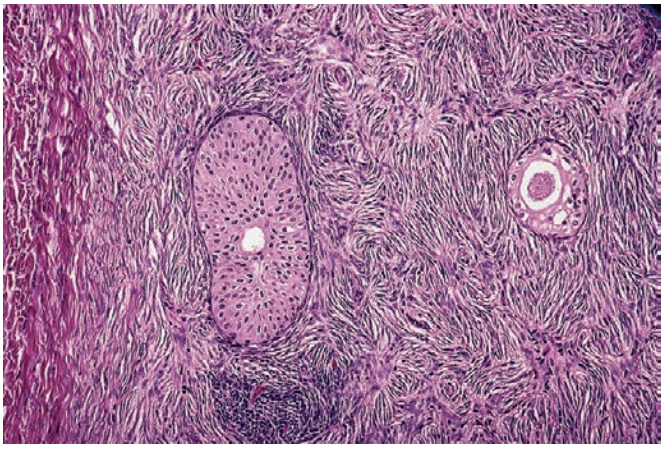

Figure 35.51 Brenner tumor of ovary showing solid and cystic epithelial cell nests embedded within fibrous tissue.

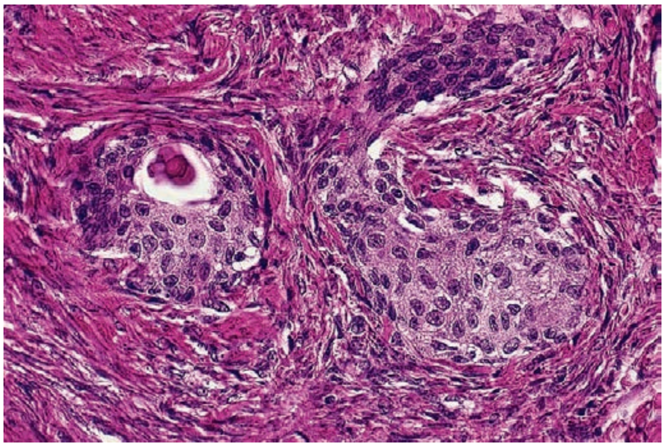

Figure 35.52 The epithelial nests of Brenner tumor are composed of cells with oval nuclei, many of which exhibit longitudinal grooves.

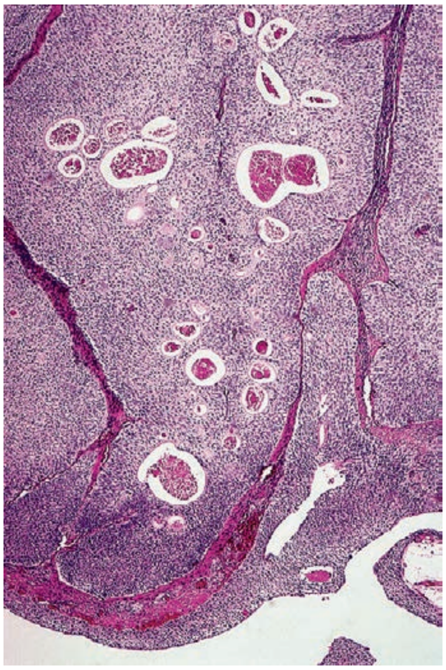

Figure 35.53 Borderline Brenner Tumor.

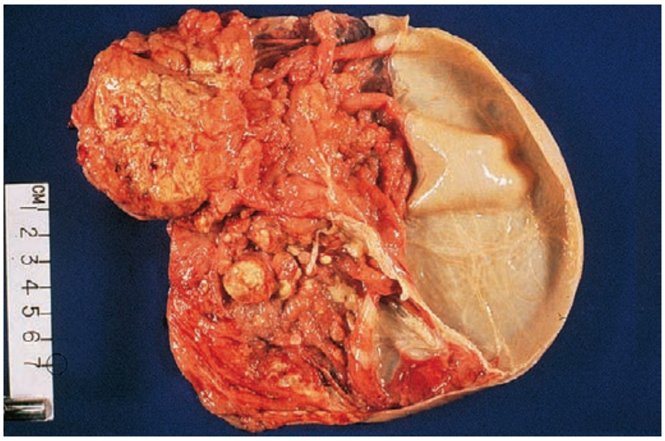

Figure 35.54 Borderline Brenner tumor showing solid area with papillary formations, associated with a large cystic space.

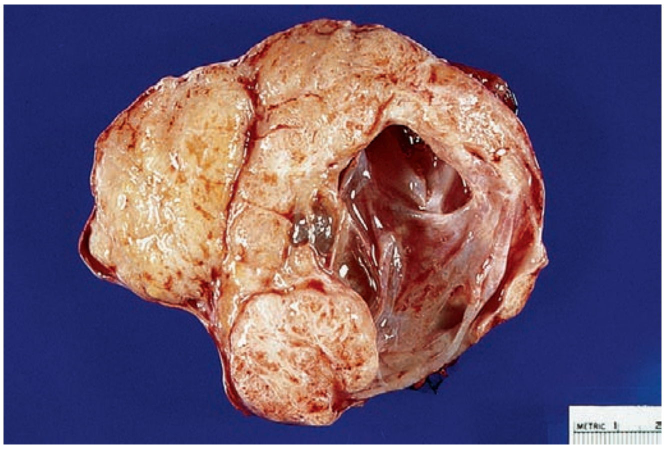

Figure 35.55 Brenner tumor with typical solid appearance coexisting with mucinous cystadenoma. This is a well-recognized combination.

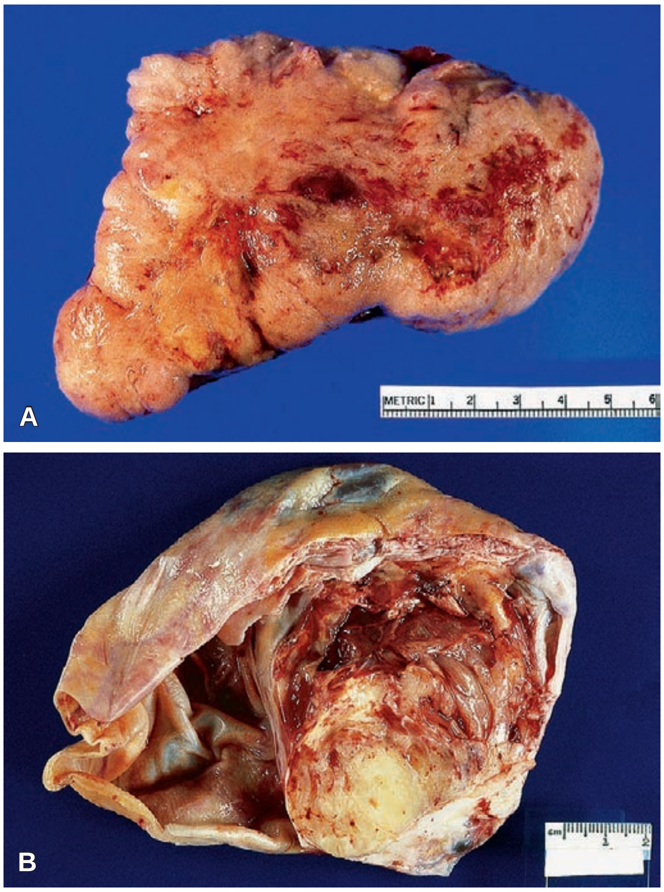

Figure 35.56 **A** and **B,** Gross appearances of carcinosarcoma of ovary. The neoplasms are large, variegated, solid and cystic, with hemorrhagic and necrotic areas.

a typical benign or borderline component.[296] The appearance of the malignant epithelium may be that of a transitional cell, squamous, glandular, or undifferentiated carcinoma, or an admixture of these.[296]

The tumors formerly referred to as **transitional cell carcinomas** (non-Brenner type),[292,297] unassociated with a benign or borderline Brenner tumor (see Fig. 35.32), are now recognized to be variants of HGSC (i.e. they are not related to Brenner tumors). Their immunophenotype is typical of HGSC (WT1 and ER expression).[298]

Brenner tumors show a strong association with mucinous tumors (Fig. 35.55)[299] and are sometimes seen together with struma ovarii.[300] Brenner tumors have exceptionally been seen to occur in accessory ovaries[301] or in other female genital tract sites, including vagina.

Carcinosarcoma and Adenosarcoma

Carcinosarcoma (malignant mixed müllerian tumor or MMMT) of the ovary resembles grossly and microscopically in every respect its more common uterine counterpart (Fig. 35.56). Thus a *homologous* variety (with nonspecific malignant stroma) and a *heterologous* variety (with malignant heterologous elements) occur.[302] The carcinomatous component may be of serous, endometrioid, squamous, or clear cell type. The sarcoma-like elements may have the appearance of chondrosarcoma (the most common), osteosarcoma, rhabdomyosarcoma, or angiosarcoma (Fig. 35.57). Hyaline droplets containing α1-antitrypsin are often present in the cytoplasm of the tumor cells.[303] Although some response to chemotherapy has been noted,[161] the overall prognosis is extremely poor,[304] with some outstanding exceptions.[305] The most reliable prognostic criterion is the initial tumor stage.[208,306–308] Unfortunately, most tumors have already extended outside the ovary at the time of surgery.[309] The most important differential diagnosis is with immature teratoma and adenosarcoma with heterologous elements. Almost all carcinosarcomas are seen in postmenopausal patients, whereas immature teratomas are typically tumors of children and adolescents. Furthermore, the former usually lack the neural and other germ cell elements of teratomas. However, cases of carcinosarcoma featuring prominent neuroectodermal differentiation have been described.[247,310,311]

Müllerian adenosarcoma, more commonly seen in the endometrium and cervix, also can occur in the ovary.[306,312–314] The morphologic appearance and behavior are again similar to those of its uterine counterpart, including the occurrence of sex cordlike elements, sarcomatous overgrowth, and heterologous elements.[313] The subject was discussed previously (see Chapter 33).

Mixed and Other Epithelial Tumors

Carcinomas composed of an admixture of two or more of the five common histotypes of ovarian carcinoma account for fewer than 1% of cases and most commonly consist of an admixture of those histotypes that are associated with endometriosis (e.g. clear cell and

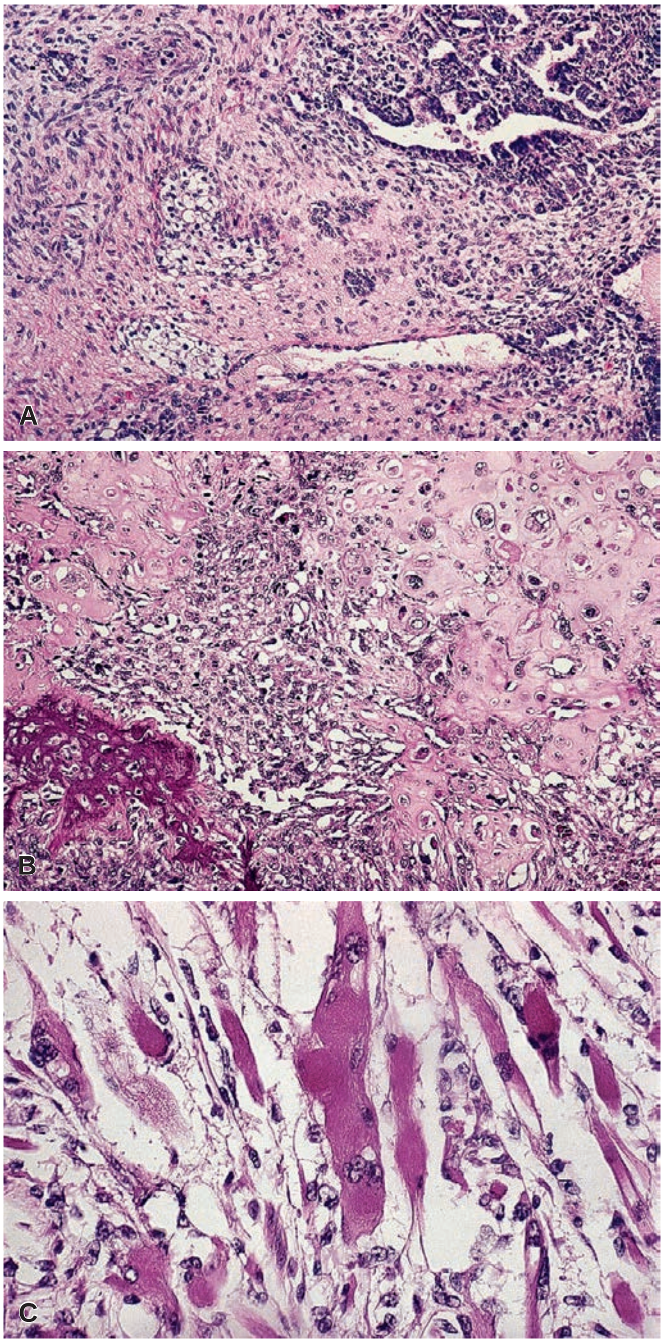

Figure 35.57 **Carcinosarcoma of Ovary.** The tumor shown in **A** is of the so-called homologous type, whereas the others exhibit heterologous foci in the form of bone and cartilage **(B)** or skeletal muscle **(C)**.

endometrioid carcinoma).[179] A diagnosis of mixed carcinoma should only be made when there is clear evidence of more than one histotype present, preferably supported by the appropriate immunostains (although they need not be done in an unequivocal case).

There are also approximately 1% of ovarian carcinomas that defy histotype classification; we refer to these as "adenocarcinoma NOS." Undifferentiated carcinoma is a diagnosis reserved for tumors that are undifferentiated throughout. Any component of HGSC, or even expression of the serous marker WT1, is sufficient to classify such a tumor as high-grade serous. Undifferentiated carcinoma, when seen in association with low-grade endometrioid carcinoma, is a de-differentiated carcinoma, following the practice for endometrial tumors.[265] Exceptionally, carcinomas of the ovary show a pattern resembling that of salivary gland carcinomas of adenoid cystic type or that of cutaneous basal cell carcinomas.[284,315,316] These may be seen in pure form or in association with conventional serous, endometrioid, or clear cell patterns. The tumors with an adenoid cystic carcinoma-like appearance are more aggressive than the basaloid neoplasms.[284]

Ovarian Carcinoma

Ovarian Tumors in Children

Germ cell tumors are the most common tumors in children, accounting for 60%–70% of all ovarian tumors in this age group.[317–319] Whereas mature cystic teratomas predominate, the proportion of malignant germ cell tumors (especially immature teratomas, yolk sac tumors, and dysgerminomas) is much greater than in adults.[320–324]

Sex cord–stromal tumors constitute 10%–25% of cases and are largely represented by juvenile granulosa cell tumor and fibrothecomas.[325] Epithelial tumors represent only 15%–20% of ovarian tumors in children, and the vast majority are benign.[326] Indisputable cases of carcinoma occur, particularly of the mucinous type; however, some cases reported as serous carcinomas actually represent yolk sac tumors or retiform Sertoli–Leydig cell tumors with a prominent papillary component, and when one encounters a malignant ovarian neoplasm in the first two decades of life, it is most probably NOT an ovarian carcinoma.

As in adults, primary malignant ovarian tumors in children need to be distinguished from metastatic neoplasms. The latter include neuroblastoma, adrenal cortical carcinoma, rhabdomyosarcoma, Ewing sarcoma, and intra-abdominal desmoplastic small cell tumor.[327]

Coexistence of Ovarian and Endometrial Carcinoma

The simultaneous presence of carcinoma in the ovary and uterus is an uncommon but well-recognized event.[328–330] The two tumors may have a similar appearance (usually endometrioid but sometimes serous or clear cell) or may be of different histologic types.[328] Theoretically, this phenomenon could be the result of: (1) metastasis from an endometrial carcinoma into the ovary; (2) two independent primary tumors; or (3) metastasis from an ovarian carcinoma to the endometrium.[329] Historically, ovarian metastasis from an endometrial tumor was favored in the presence of high-grade (especially serous), advanced stage, bilaterality, and/or very small size of the ovarian tumor, involvement of the tubal lumen, and presence of deep myometrial invasion and/or vascular invasion in the uterine tumor.[328] It was thought that most neoplasms with a low-grade endometrioid appearance in both sites were probably independent neoplasms, as they are associated with little or no myometrial invasion in the uterus, extrauterine disease confined to the ovary (without ovarian surface involvement or trans-coelomic spread), and often endometriosis. These patients have an excellent prognosis, even without adjuvant therapy, as would be expected for synchronous stage Ia tumors. It was surprising, then, to find that based on sequencing of tumor DNA, the endometrial and ovarian tumors in a large majority of such cases are derived from a single clone.[331,332] The compelling molecular evidence that these tumors are clonally related does not, of course, change the excellent prognosis and it is therefore reasonable to continue with the previous practice of staging such low-grade organ-confined tumors as independent primary tumors, as that reflects their behavior. A further interesting point is that patients with synchronous endometrial and ovarian carcinoma have Lynch syndrome in only 7% of cases.[333]

Cytology

The main role of diagnostic cytology in ovarian carcinoma is the identification of malignant cells in the peritoneal cavity. The value of peritoneal washing cytology to detect the microscopic spread of ovarian carcinoma has been acknowledged by the fact that the FIGO staging system incorporates the results of cytological examination of the washings in its scheme. Serous carcinomas are more often positive than carcinomas of other types, and high-grade tumors more than low-grade tumors.[334] Specifically, a high positive rate is related to advanced stage of disease, involvement of the ovarian surface, a moderate to large amount of fluid, and nonbloody serous ascites.[335]

The interpretation of peritoneal washings can be made difficult by the admixture of reactive mesothelial cells as well as the differential diagnosis with peritoneal malignant mesothelioma. Calretinin is a good positive marker of mesothelioma, while BerEP4 is consistently positive in carcinomas, but also stains occasional mesotheliomas.[336,337] It should be noted that the "epithelial/carcinoma" markers such as BerEP4 and MOC31 do not allow distinction between carcinoma and benign epithelium (e.g. derived from endometriosis) as both can stain positively. Heterozygous loss of 9p21 is specific for mesothelioma, but not completely sensitive.[336]

Therapy

The primary form of therapy of epithelial tumors is surgical.[338–340] Benign tumors are cured by a conservative operation in the form of unilateral salpingo-oophorectomy. Although the uninvolved portion of the ovary can be preserved for some small benign tumors, the majority require the excision of the entire gonad. Most borderline tumors in young females can also be treated conservatively with safety, the results following salpingo-oophorectomy being equivalent to those seen following more extensive procedures.[341,342] As a matter of fact, some cases have been treated with cystectomy only, the overall outcome being excellent; however, recurrences in the ipsilateral ovary are relatively common and close follow-up is necessary.[343]

Carcinomas were traditionally treated initially by bilateral salpingo-oophorectomy with total abdominal hysterectomy and omentectomy, peritoneal washings, peritoneal biopsies, and lymph node dissection (so-called complete surgical staging), irrespective of histotype. There has been some move away this more extensive surgical staging as it is clear that patients with "apparently" low stage (stage Ia) mucinous and endometrioid carcinomas do exceptionally well, even without extensive staging or adjuvant therapy. Avoiding the morbidity of more extensive surgery and chemotherapy for these two subtypes does not significantly impact on their excellent prognosis (>95% disease-free survival at 5 years).[344] On the other hand, patients with HGSC have such a guarded prognosis that, to date, it has not been possible to identify a group where chemotherapy would not be offered, in the absence of medical contraindications. Thus, more extensive surgery, including node dissection, is not needed to guide treatment for these patients as all will receive platinum/taxane chemotherapy (with intraperitoneal delivery in some patients)[338] irrespective of nodal status. At the present time, most patients with ovarian carcinoma have something less than complete surgical staging.

A recent trend is towards neoadjuvant chemotherapy for patients with advanced stage ovarian carcinoma. As noted previously, most such tumors are HGSC. A large international randomized clinical trial found that neoadjuvant chemotherapy followed by surgery, rather than surgery first, resulted in comparable survival rates and less morbidity.[345] This approach is becoming more widely accepted; only those patients who experience a response to chemotherapy go on to surgery, and in this interval debulking specimen there is the opportunity to assign a chemotherapy response score (CRS), as an indication of response to neoadjuvant chemotherapy.[346] CRS is assigned based on examination of the omentum, as follows: CRS1: mainly viable tumor with no or minimal regression-associated fibroinflammatory changes limited to a few foci, CRS2: appreciable tumor response amidst viable tumor, CRS3: no residual tumor OR minimal irregularly scattered tumor foci seen as individual cells, cell groups or nodules up to 2 mm in maximum size. Only CRS3 is prognostically significant, and these patients, as one would expect, are more likely to be long-term survivors.[346]

Prognosis

The overall prognosis of ovarian carcinoma remains poor. HGSC accounts for most cases, most of which are advanced stage at presentation, and a large majority of these patients will die of disease. Stage and histotype are of independent prognostic significance (even though they co-vary, as noted in Table 35.2). Assignment of grade in ovarian carcinoma is done in a histotype-specific way.[347] Grade is not assigned in HGSC, low-grade serous carcinoma or clear cell carcinoma. Grading systems for the latter have been proposed but have not been independently validated to be of prognostic significance independent of stage. Endometrioid carcinomas are typically graded using the FIGO system in use for endometrial carcinomas of endometrioid type, while mucinous carcinomas are most commonly graded using the WHO system, which does not provide specific criteria for grading.

Germ Cell Tumors

Germ cell tumors constitute approximately 20% of all ovarian neoplasms. Most of them are seen in children and young adults, and approximately 95% are benign cystic teratomas; the younger the patient, the more likely the germ cell tumor will be malignant.[328,348]

Significant advances have been made in the understanding of these tumors,[349,350] many of them fueled by the description of new immunohistochemical markers having a high degree of specificity for germ cell tumors in general and for some of the individual types.[351–353]

In the sections that follow, the tumors are discussed as individual types; however, it should be recognized that a combination of various elements occurs in approximately 8% of cases. These are referred to as *mixed germ cell tumors*[354,355]; the most common combination is that of dysgerminoma with yolk sac tumor, but many others occur,[356] including some with a predominance of the polyembryoma component.[348]

One of the greatest achievements in oncology is represented by the therapy of malignant germ cell tumors. Chemotherapeutic regimens consisting of a combination of bleomycin, etoposide, and cisplatin have resulted in overall disease-free survival rates greater than 95%.[357,358]

Dysgerminoma

Dysgerminoma constitutes less than 1% of all ovarian tumors.[359] Most patients are young. In Santesson's series of nearly 300 cases, 81% were under 30 years of age and 44% were under 20 years of age.[360] Dysgerminoma made up 6% of 188 childhood ovarian neoplasms collected by Abell et al.[361] Approximately 5% of dysgerminomas arise in abnormal gonads: pure or mixed gonadal dysgenesis (from a gonadoblastoma) or testicular feminization (androgen insensitivity) syndrome. Exceptionally, the tumor is associated with hypercalcemia.[362]

Dysgerminoma is somewhat more common on the right side and is bilateral in 15% of cases.[360] It is often large (it may reach

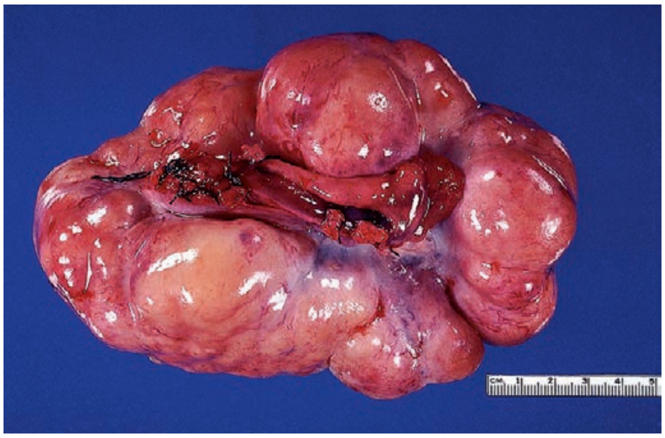

Figure 35.58 Typical lobulated outer aspect of ovarian dysgerminoma.

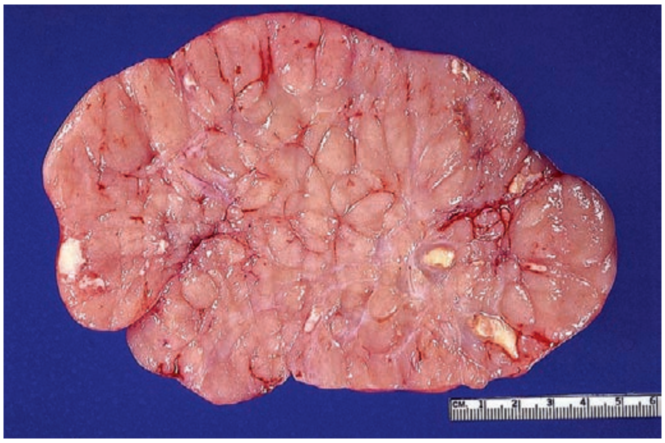

Figure 35.59 **Cut Surface of Ovarian Dysgerminoma.** The multinodular solid quality and the tan color are characteristic features.

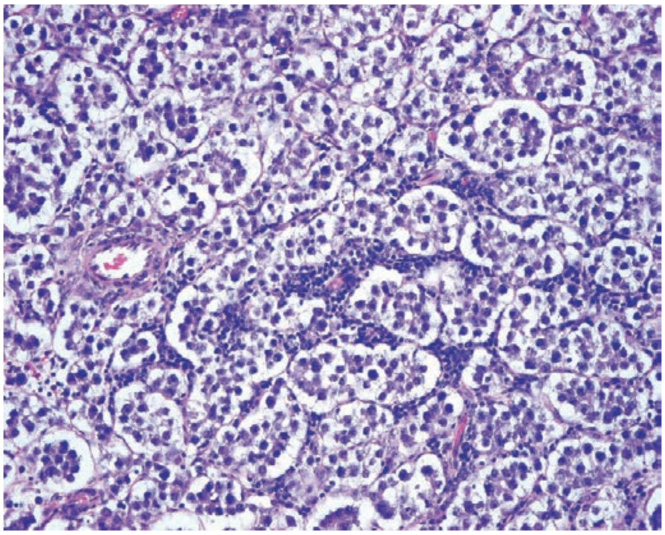

Figure 35.60 Typical nesting appearance of ovarian dysgerminoma. The septa contain numerous inflammatory cells.

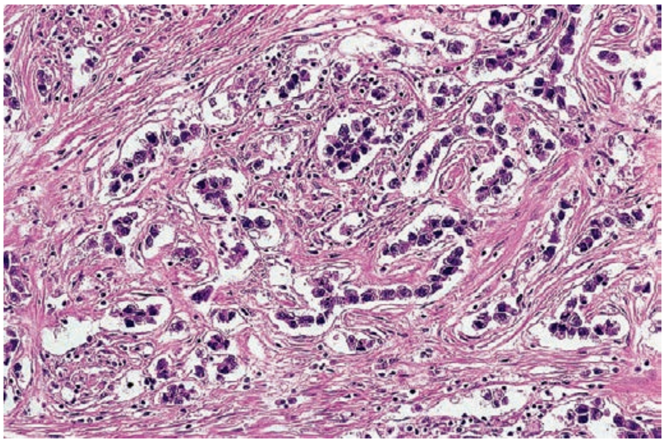

Figure 35.61 The thin trabecular pattern that dysgerminomas sometimes exhibit may be the source of diagnostic errors.

over 1000 g) and encapsulated, with a smooth, often bosselated surface (Fig. 35.58). The cut surface is solid and gray; foci of hemorrhage and necrosis can occur, but they are not as common or prominent as in other malignant germ cell tumors (Fig. 35.59). Microscopically, the tumor cells usually group themselves in well-defined nests separated by fibrous strands infiltrated by lymphocytes (most of which are T cells[363]; Fig. 35.60). Occasionally, a pseudotubular, alveolar, or cordlike arrangement may be seen (the latter particularly at the tumor periphery), which may be quite confusing (Fig. 35.61).[364] Focal necrosis, hyaline changes in vessels, germinal centers, and granulomatous foci may be present. The individual tumor cells are uniform and have large "squared-off" nuclei, *one or more prominent elongated purple nucleoli*, and abundant clear to finely granular cytoplasm that contains glycogen and sometimes fine droplets of fat. The cell membrane is prominent.

Immunohistochemically, the tumor cells are consistently reactive for PLAP and CD117, variably for keratin (erratically and focally), and sometimes for GFAP and desmin but not for CD30.[365–368] OCT4, a transcription factor involved in the regulation of pluripotency during embryonic development, stains the cells of dysgerminoma, the germ cell component of gonadoblastoma, and embryonal carcinoma, but not yolk sac tumor.[369] SALL4 is typically positive.[370]

The microscopic pattern, ultrastructural appearance, immunohistochemical and cytogenetic profiles, clinical behavior, and probable histogenesis (from indifferent or primordial germ cells) of ovarian dysgerminoma are the same as for classic seminoma of the testis.[371–373] It also commonly shows cytogenetic abnormalities involving chromosome 12p. Like testicular seminoma, ovarian dysgerminoma may exhibit signs of early differentiation toward other types of germ cell elements. These include:

1. Scattered hCG-positive syncytiotrophoblastic cells, often in close proximity to blood vessels or to hemorrhagic foci (Fig. 35.62).[374] This change, seen in approximately 3% of all dysgerminomas, may be accompanied by serum elevation of hCG and tissue immunoreactivity for this marker.
2. Abortive yolk sac elements, accompanied by serum elevation of alpha-fetoprotein and tissue immunoreactivity for this marker (Fig. 35.63).[375]

As with the equivalent testicular examples, it is not clear whether these changes alter the prognosis of dysgerminoma, and it is, therefore, important to distinguish them from dysgerminoma admixed with choriocarcinoma, embryonal carcinoma, or yolk sac tumor, a phenomenon that occurs in approximately 8% of cases and that affects prognosis significantly.

Metastases of dysgerminoma occur more commonly in the contralateral ovary, retroperitoneal nodes, and peritoneal cavity.

The survival rate of pure dysgerminoma is 95%. The initial treatment of unilateral dysgerminoma is oophorectomy. Chemotherapy is the treatment of choice for this tumor when it has spread beyond the ovary.

Yolk Sac Tumor and Embryonal Carcinoma

The history of these two germ cell neoplasms of the ovary is replete with confusing, contradictory, and sometimes erroneous statements as to their origin, relationship, and natural history. Yolk sac tumor was included in Schiller's original description of mesonephroma,[376] together with the ovarian tumor presently designated as clear cell carcinoma.[377] Once it was realized that the latter has a different histogenesis, morphologic appearance, and natural history, the analogy became no longer tenable. The next generation of articles on the subject clearly separated these two neoplasms but used more or less interchangeably the terms *yolk sac tumor* and *embryonal carcinoma*. Since both of these neoplasms are of germ cell derivation, share many morphologic features, and are closely related histogenetically, this is not entirely inappropriate.[378] However, enough differences exist between the two to justify their separation.

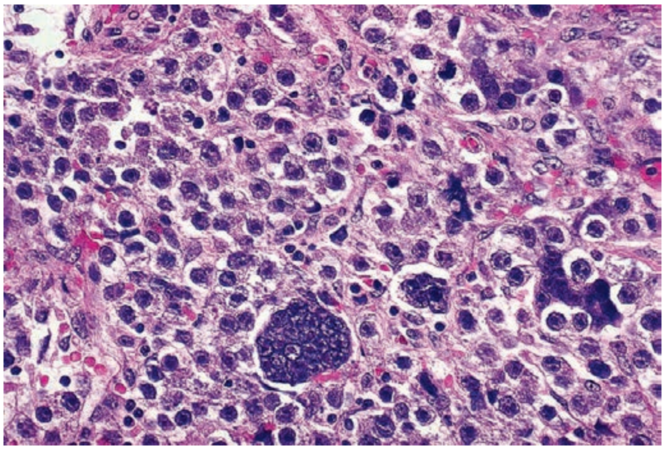

Figure 35.62 Isolated multinucleated cells of trophoblastic type in ovarian dysgerminoma.

Yolk sac tumor (endodermal sinus tumor) is generally a neoplasm of children and young adults (median age, 19 years).[379] In the series of Kurman and Norris,[380] 23% of the patients were prepubertal at the time of diagnosis. None of the patients presented with precocious puberty, amenorrhea, or hirsutism. Vaginal bleeding occurred in only 1%. The serum alpha-fetoprotein level was invariably elevated, whereas the chorionic gonadotropin levels were normal, resulting in consistently negative pregnancy tests. Grossly, the tumors had an average diameter of 15 cm, a smooth and glistening external surface, and a variegated cut surface, partially cystic and often containing large foci of hemorrhage and necrosis (Fig. 35.64). A component of benign cystic teratoma was identified in 10 of the 71 cases.

Exceptionally, a yolk sac tumor will be found in the pelvis (in close proximity to the uterus), omentum, or mesentery, unattached to the ovary.[381–383]

Microscopically, the appearance of yolk sac tumors is extremely variable.[384] There are reticular or microcystic areas formed by a loose meshwork lined by flat or cuboidal cells (Fig. 35.65), rounded or festooning pseudopapillary processes with central vessels (Schiller–Duval bodies), and solid areas. The mesenchyme-like component of these tumors has pluripotential properties; it usually presents in the form of spindle cells in a well-vascularized myxoid background, but it exhibits keratin immunoreactivity as a sign of early epithelial differentiation and may contain heterologous elements such as skeletal muscle.[385]

Intracytoplasmic and extracellular PAS-positive hyaline droplets are nearly always present. Their chemical composition is heterogeneous; they usually stain for alpha-fetoprotein, but they may also

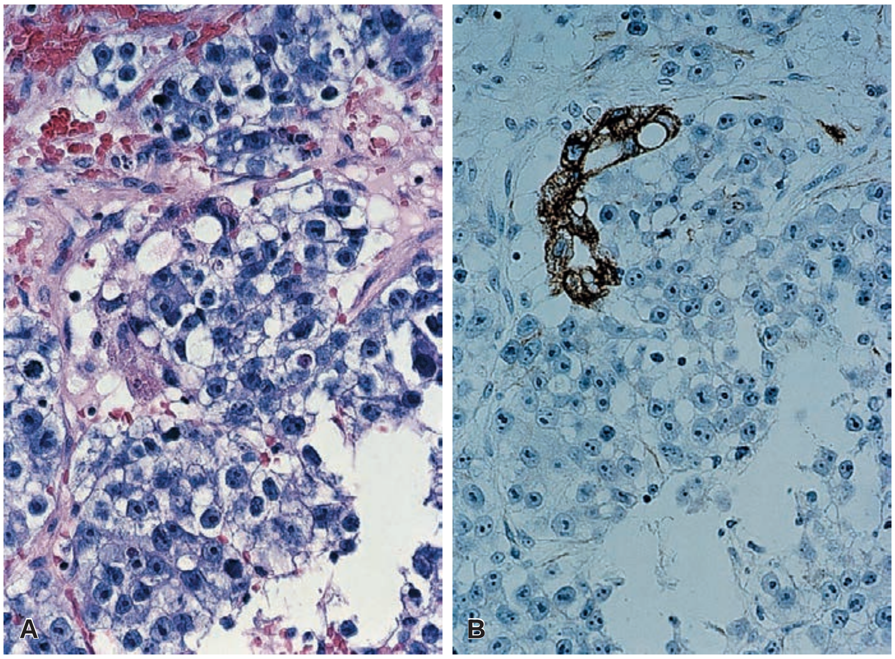

Figure 35.63 **Ovarian Dysgerminoma With Early Yolk Sac Differentiation. A,** H&E appearance. The foci of early yolk sac differentiation are represented by the small gland-like structures near the center. **B,** This formation is strongly immunoreactive for keratin, in contrast with the rest of the neoplasm. (Courtesy of Dr. Vinita Parash, New Haven, CT.)

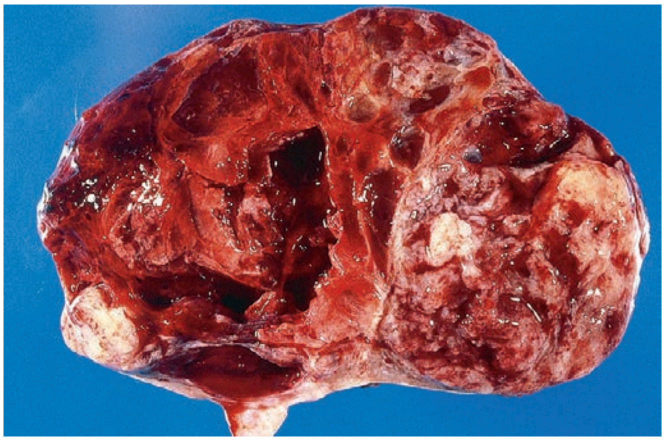

Figure 35.64 Gross appearance of yolk sac tumor. The cut surface is remarkably heterogeneous due to extensive hemorrhage, necrosis, and cystic degeneration.

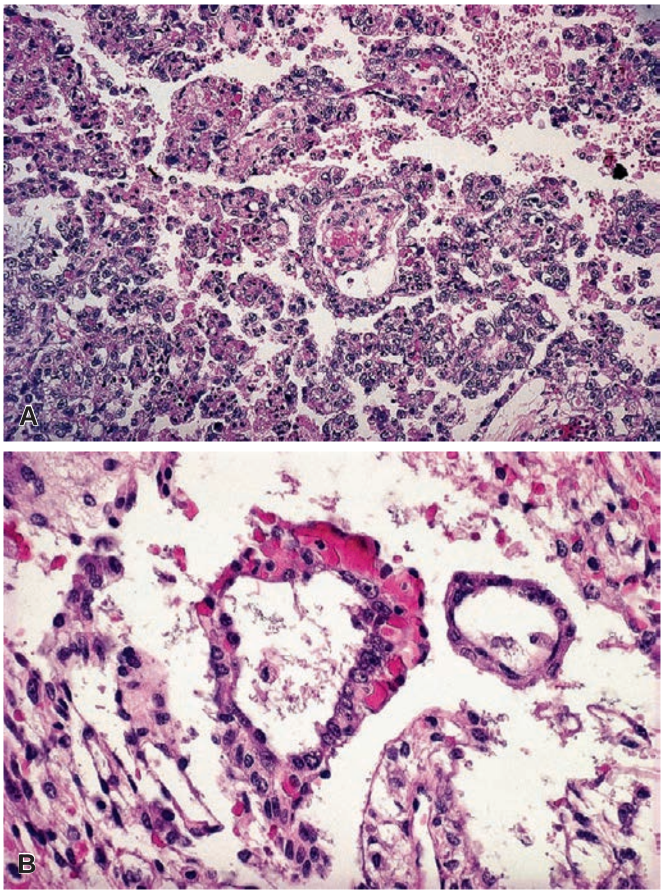

Figure 35.65 **A** and **B,** Low- and high-power views of ovarian yolk sac tumor. Numerous hyaline globules are seen in the cytoplasm of the tumor cells lining the papillae.

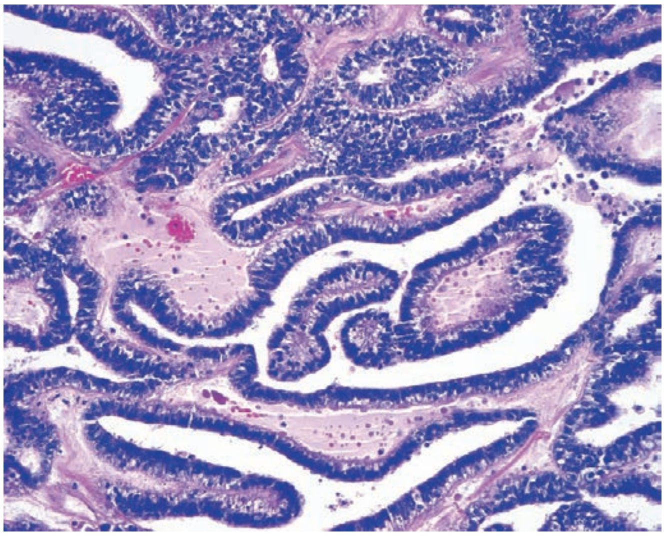

Figure 35.66 Yolk sac tumor with endometrioid features.

contain α1-antitrypsin and basement membrane components (type IV collagen and laminin).[386] Yolk sac tumor also stains for pankeratin but not for keratin 7 or EMA (in contrast with endometrioid and clear cell ovarian carcinoma), or for WT1 (in contrast with serous ovarian carcinoma).[387] They also exhibit positivity for SALL4 and glypican 3,[388] a property they share with testicular and extragonadal yolk sac tumors.[389] However, OCT4 is typically negative. DNA ploidy studies have shown that yolk sac tumors are almost invariably aneuploid.[390]

A fourth of the yolk sac tumors have vesicular structures with eccentric constrictions surrounded by a dense spindle cell stroma; this has been referred to as a *polyvesicular vitelline pattern* and is said to be associated with a good prognosis when present in a pure form.[391] Others show a scattered hCG-positive syncytiotrophoblast component. Still others exhibit evidence of differentiation toward hepatic, intestinal, and parietal yolk sac structures.[392] The latter are recognized by the presence of thick layers of intercellular basement membrane.[393] The *hepatoid* component, which can predominate almost to the exclusion of the others, is composed of masses, nests, and broad bands of large polyhedral cells with occasional glandular formations and numerous hyaline bodies. Their immunohistochemical profile is similar to that of hepatocellular carcinoma, including reactivity for α1-antitrypsin and a canalicular staining pattern with polyclonal CEA.[394,395] These hepatoid yolk sac tumors are to be distinguished from *hepatoid ovarian carcinomas*, rare tumors of epithelial origin.[396] In some yolk sac tumors, the presence of *glandular* formations may simulate the appearance of endometrioid carcinoma (Fig. 35.66).[397] An exceptional event in ovarian yolk sac tumor is the presence of mucinous carcinoid tumor as a manifestation of endodermal differentiation.[398]

Areas of luteinized stromal cells may be present and may sometimes be responsible for virilization.

An important phenomenon in the differential diagnosis of yolk sac tumor of germ cell origin is the occurrence of typical yolk sac tumor in older women, sometimes in association with an epithelial malignancy such as clear cell carcinoma.[399] These yolk sac tumors of presumed somatic cell origin are analogous to the well-known phenomenon of choriocarcinomatous differentiation in poorly differentiated carcinomas from a number of different primary sites[400] and should be distinguished from yolk sac tumors of germ cell origin. The patient's age can usually serve to make this distinction as those of somatic cell origin arise in the elderly.

Teilum's brilliant hypothesis that this tumor recapitulates normal yolk sac elements[377] has been amply confirmed by histochemical and ultrastructural studies,[401–403] including the detection of GATA4, a transcription factor that regulates the differentiation and function of murine yolk sac endoderm.[404]

In the series of Kurman and Norris,[380] from more than 40 years ago, the actuarial survival at 3 years was only 13%; although 71%

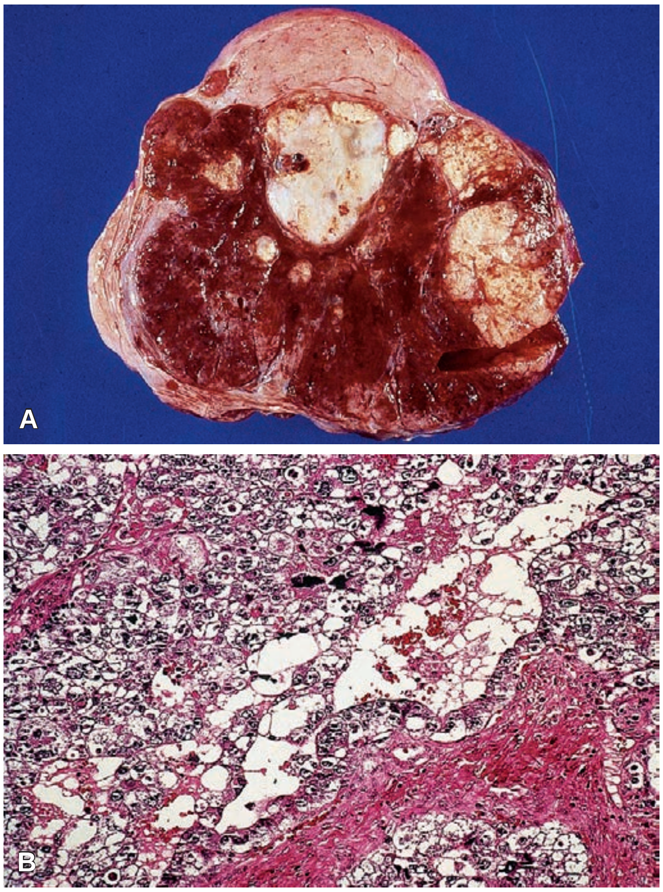

Figure 35.67 **A** and **B**, Gross and microscopic appearance of embryonal carcinoma of ovary.

of the patients were thought to have stage I tumors, subclinical metastases were present in 84%. The introduction of multidrug chemotherapy has dramatically improved survival rates.[405] As usual, clinical stage is the most important prognostic indicator.[385,406] Serial determinations of serum alpha-fetoprotein are useful in monitoring the tumor course.[407,408]

Embryonal carcinoma also occurs in a young age group (median age, 15 years). In one series, 47% of the patients were prepubertal at the time of diagnosis, and 43% of them presented with precocious puberty.[409] Vaginal bleeding was recorded in 33%, amenorrhea in 7%, and hirsutism in 7%. Serum chorionic gonadotropin levels are invariably high, to a level that may result in consistently positive pregnancy tests.

Grossly, the median diameter of these neoplasms is 17 cm, on average. Their external surface is smooth and glistening, and their cut surface is predominantly solid and variegated, with extensive areas of necrosis and hemorrhage (Fig. 35.67). Microscopically, this tumor has a similar appearance to the embryonal carcinoma of the adult testis. As such, it is composed of solid sheets and nests of large primitive cells, occasionally forming papillae and abortive glandular structures (see Fig. 35.67). Syncytiotrophoblast-like tumor cells are frequently seen scattered among the smaller cells; these are immunoreactive for hCG. Embryonal carcinoma shows immunoreactivity for pan-keratin, CD30, OCT4, and SALL4.[410] In the Kurman and Norris series,[421] the prognosis was somewhat better than for yolk sac tumor, but current multidrug chemotherapeutic regimens have erased these differences.[380,411]

Embryonal carcinomas largely composed of embryoid bodies are referred to as *polyembryomas*.[360]

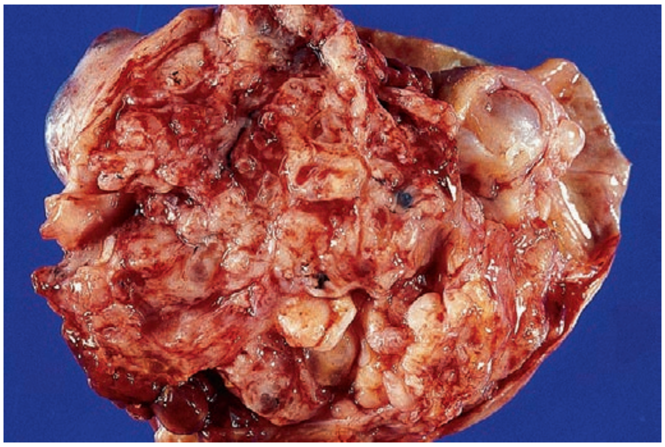

Figure 35.68 Gross appearance of ovarian immature teratoma.

Choriocarcinoma

Most choriocarcinomas involving the ovary represent metastases from uterine tumors. The exceedingly rare primary ovarian choriocarcinomas can develop from an ovarian pregnancy (gestational type, which is the most common) or as a form of germ cell neoplasm (nongestational).[412] The latter can be pure or, more frequently, a component of a mixed germ cell tumor. If pure, DNA typing may be required to distinguish between a gestational choriocarcinoma, containing paternal DNA, and nongestational choriocarcinoma of maternal germ cell origin. Microscopically, they show the typical admixture solid cytotrophoblastic elements enveloped by a rim of syncytiotrophoblast, often in a necrotic and hemorrhagic background. This should be distinguished from aggregates of syncytiotrophoblasts admixed with other germ cell elements (e.g. yolk sac tumor or embryonal carcinoma), which should not alter the diagnosis. Immunohistochemical reactivity for hCG is the rule.

Ovarian choriocarcinomas of either gestational or nongestational type should be distinguished from the exceptionally rare ovarian carcinomas of epithelial origin exhibiting choriocarcinomatous differentiation, a phenomenon analogous to that sometimes seen in carcinomas of the lung, breast, endometrium, gallbladder, and other sites.[413] Patients with choriocarcinomatous differentiation arising in an epithelial malignancy are typically considerably older than those with ovarian choriocarcinoma of either germ cell or gestational origin.

Ovarian gestational choriocarcinomas have a better prognosis than their nongestational counterparts.[400]

Immature Teratoma

Immature teratoma is the currently preferred term for the malignant ovarian teratoma usually seen in children and adolescents and composed of a mixture of embryonal and adult tissues derived from all three germ layers, regardless of its gross appearance (Fig. 35.68). Any type of tissue may be represented. The main component is usually neuroepithelial, but mesodermal elements are also common (Fig. 35.69).[414] Some tumors are predominantly composed of endodermal derivatives, including esophagus, liver, and intestinal structures.[415]

Staining for GFAP is helpful in the identification of mature and immature glial tissue.[416] It should be noted, however, that GFAP is also detectable in chondrocytes.[417]

Grossly, immature teratoma may be solid throughout, solid with multiple minute cysts, or predominantly cystic. Grading of immature

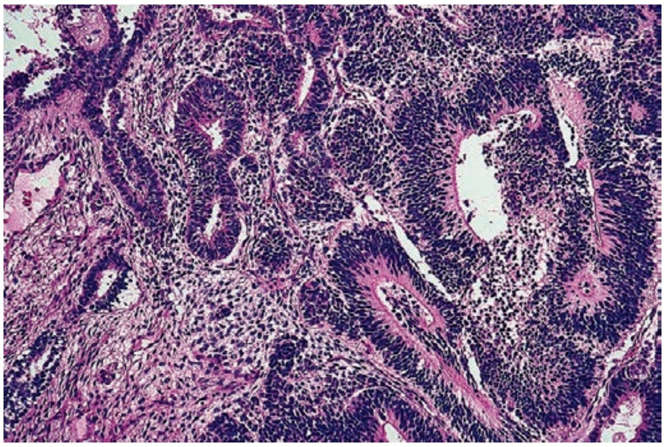

Figure 35.69 Ovarian immature teratoma with predominance of primitive neuroepithelial elements.

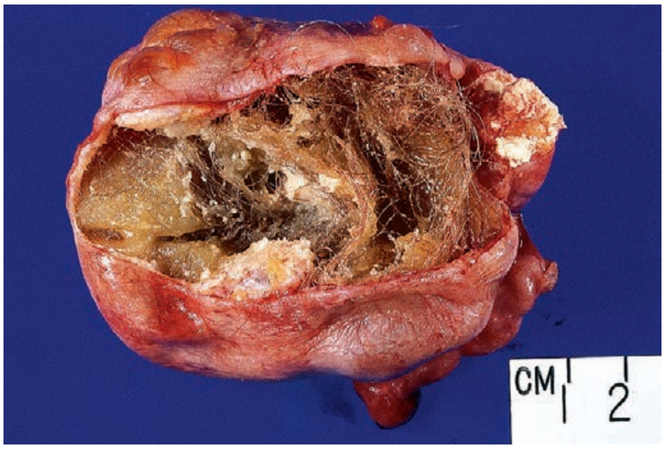

Figure 35.70 Admixture of sebum and hair within the cavity of an ovarian mature cystic teratoma.

teratomas is done based on the WHO 2014 recommendations; grade 1 immature teratomas behave in a benign fashion, while grade 2 and 3 immature teratomas are malignant and can be referred to collectively as "high-grade" immature teratoma. The grading system is as follows:

Grade I, Rare foci of immature neuroepithelial tissue (<1 low power field in any slide)
Grade II, Occasional foci of immature neuroepithelium with mitoses, *not exceeding* three low power fields in any one slide
Grade III, Few or no mature tissues; numerous neuroepithelial elements, merging with a cellular stroma *occupying* four or more low power fields per slide.

Obviously, a thorough tumor sampling is necessary for this grading system to be accurate.

It is important to separate from this group the teratomas that also have yolk sac or embryonal carcinoma patterns.[418] On occasion, an ovarian immature teratoma can be predominantly or exclusively composed of one type of tissue. Neoplasms with an exclusive or almost exclusive malignant neuroectodermal composition are designated **malignant neuroectodermal tumor** and are generally regarded as a form of monodermal teratoma.[419,420] A variation on the theme is the ovarian **ependymoma**, in which this neuroectodermal component is made up entirely of primitive ependymal structures.[420–422] Other teratomas have a prominent component of renal (metanephrogenic),[423] retinal anlage,[424] or skeletal muscle (rhabdomyosarcomatous) nature.[425]

A sometimes confusing pattern seen in teratomas, usually in connection with the neuroectodermal component, is the presence of florid vascular proliferation,[426] a phenomenon possibly due to the secretion of angiogenic factors by the tumor cells and which has also been recorded at other sites.[427]

Another peculiar morphologic change sometimes encountered in these tumors is membranous fat necrosis, perhaps secondary to torsion and ischemia.[428]

The treatment of immature teratoma consists of surgery plus multidrug chemotherapy for grade 2 or grade 3 tumors[429–431]; sometimes, only mature tissue is found in metastatic sites following chemotherapy, a sign of excellent prognosis.[416] It is interesting, however, that the abnormal karyotype of the original immature teratoma is maintained in the area of chemotherapy-induced maturation.[432] This mature tissue may continue to grow (the growing teratoma syndrome, more commonly observed with testicular germ cell tumors), but the growth is self-limited if all tissues are mature and masses formed can be observed, without further treatment.[433]

Mature Solid Teratoma

Mature solid teratoma has a predominantly solid gross appearance, but multiple small cystic areas also are present. By definition, the tumor should be *composed entirely of adult tissues* derived from all three germ layers.[434,435]

Clearly, extensive sampling is needed to separate this tumor from a grade 1 immature teratoma. The two tumors are closely related, and the distinction is somewhat subjective; as a matter of fact, some authors refer to mature solid teratoma as "grade 0" immature teratoma.

This rare neoplasm occurs in young women, predominantly in the second decade. The prognosis is excellent, even if peritoneal implants (also mature and for the most part glial in composition) are present.[436]

Mature Cystic Teratoma

Mature cystic teratomas make up almost 20% of all ovarian neoplasms. They constitute the most common ovarian tumor in childhood.[332] They are unilateral in 88% of cases and typically provoke only symptoms relating to the mass. Occasionally, however, they are accompanied by hemolytic anemia,[437,438] virilization,[439,440] or paraneoplastic encephalitis.[441] The latter is often associated with autoantibodies against N-methyl-D-aspartate (NMDA) receptor; teratoma (mature or immature) is the most common neoplasm found in association with this particular paraneoplastic syndrome, and resolution of symptoms, consisting of psychiatric manifestations and/or neurological deficits, occurs in most patients after removal of the teratoma. A moving account of this condition, from the patient's perspective, is provided in the memoir "Brain on Fire" by Susannah Cahalan. Grossly, they are usually multiloculated. The cystic content is greasy, largely composed of keratin, sebum, and hairs (Fig. 35.70). Teeth are often present (Fig. 35.71).[442] Sometimes the tumor contains an imperfectly formed mandible or even a partial human body-like structure (homunculus); the latter are referred to as *fetiform teratomas*.[443] The teeth tend to be located in a well-defined nipple-like structure covered with hair, known as *Rokitansky's protuberance*. This structure should be selected for microscopic examination (even if

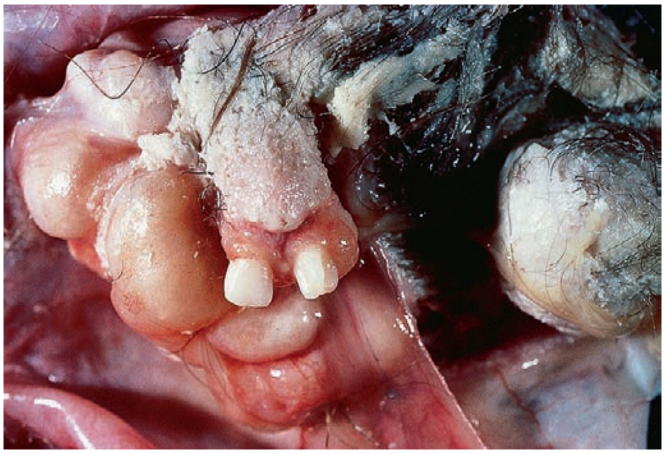

Figure 35.71 Well-developed teeth in ovarian mature cystic teratoma.

decalcification may be required) because it will exhibit the greatest variety of tissue types.

In a classic microscopic study, Blackwell et al.[444] found ectodermal derivatives in 100% of the tumors, mesodermal structures in 93%, and endodermal derivatives in 71%. The cystic cavities are lined by mature epidermis. Skin appendages and neural (particularly glial) tissue are extremely common. The latter may feature meningothelial proliferations and Wagner–Meissner corpuscles and be accompanied by florid vascular proliferation.[445,446] Other common tissue types present are cartilage, respiratory tissue, and gastrointestinal tract tissue (Fig. 35.72). The gastric mucosa can be very well developed anatomically, to the point of containing interstitial cells of Cajal[447]; sometimes it is complicated by peptic ulcer formation.[448] Other tissues include thyroid (10% of cases), various types of melanin-containing tissue (particularly patients with dark skin),[449] anterior pituitary,[450] various types of neuroendocrine cells,[451] prostate,[452,453] pancreas, and cavernous blood vessels. Prominent lymphoid infiltration of glial elements, with germinal center formation, is a feature of teratomas associated with NMDA receptor paraneoplastic syndrome; occasionally the syndrome becomes manifest after removal of the teratoma.[441]

Because of the usual predominance of skin and skin adnexal structures, and also on historical grounds, some authors still prefer the old term dermoid cyst for ovarian mature cystic teratoma. Time-honored considerations aside, we feel that this term is pathogenetically not very informative and that it does not do justice to the plethora of other tissue types that can be present in these tumors.

By definition, all of the components present in mature cystic teratomas should appear histologically mature. However, on occasions one sees microscopic foci of immature (to be distinguished from malignant, see later) tissue in them. The behavior of these tumors, which can be considered to be grade 1 immature teratomas, is usually benign, with no further treatment required beyond surgical removal.[454]

Mature cystic teratomas may coexist with Brenner tumor and thecoma.[455,456]

On occasion, teratomas rupture into the abdominal cavity; when this occurs, the keratin and sebum present in the lumen may provoke a prominent foreign body reaction that can look like metastatic cancer to the surgeon, who may be incredulous when the surgical pathologist goes back to him or her with a benign diagnosis (but not incredulous enough to accept a risky bet about it; Fig. 35.73).[457,458]

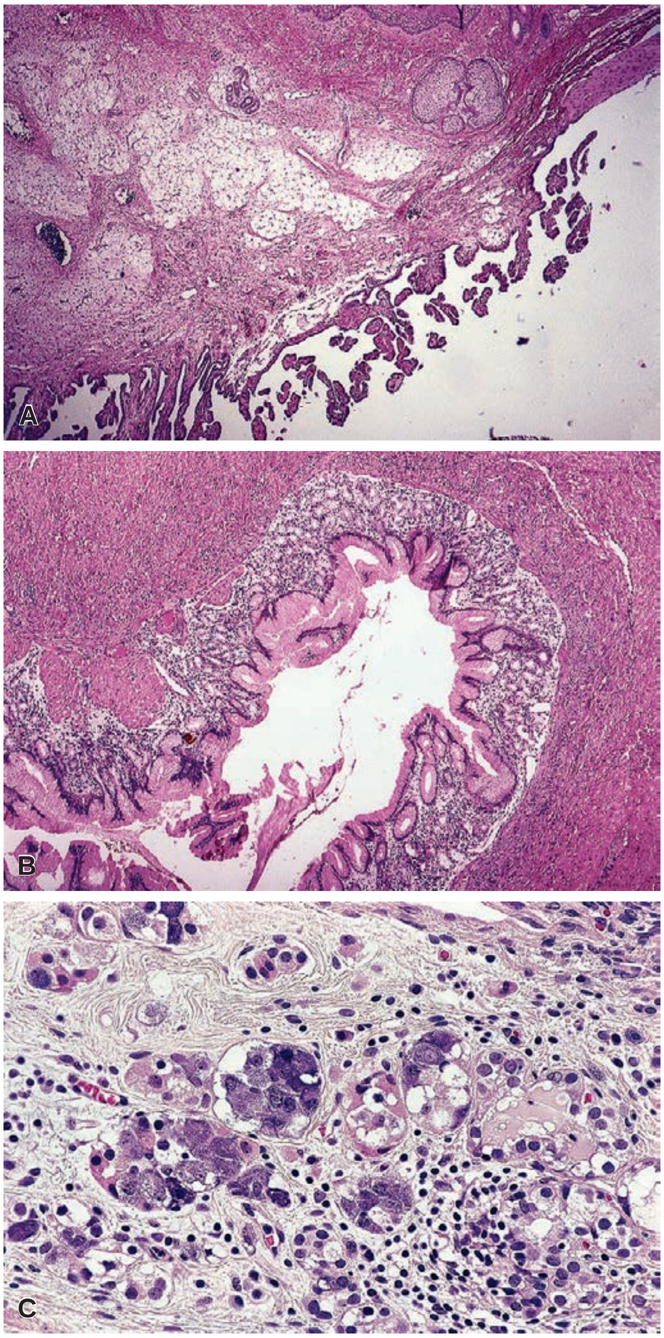

Figure 35.72 Various Tissue Components of Mature Cystic Teratoma of Ovary. A, Skin adnexa, glial tissue, and choroid plexus; **B,** gastric mucosa of pyloric type; **C,** anterior pituitary gland.

In other instances, mature ovarian teratomas of either the cystic or solid variety—as well as immature teratomas—may be accompanied by peritoneal nodules exclusively composed of mature glial and neuronal tissue, a condition known as *gliomatosis peritonei* (Fig. 35.74).[459–462] These nodules appear grossly as miliary grayish-white nodules in the peritoneal surface or omentum and may be accompanied by fibrosis and chronic inflammation. This is a benign process, as long as the glial tissue is entirely mature and unaccompanied by other teratomatous elements (Fig. 35.75).[463–465] Another teratoma-related process is peritoneal "melanosis," which can also follow the rupture of a cystic teratoma.[466]

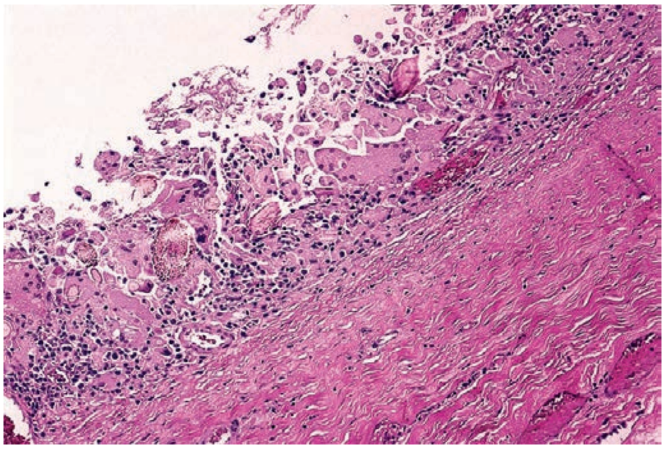

Figure 35.73 Exuberant foreign body-type giant cell response to contents of ruptured ovarian mature cystic teratoma. These changes may simulate grossly the appearance of tuberculous peritonitis or metastatic carcinoma.

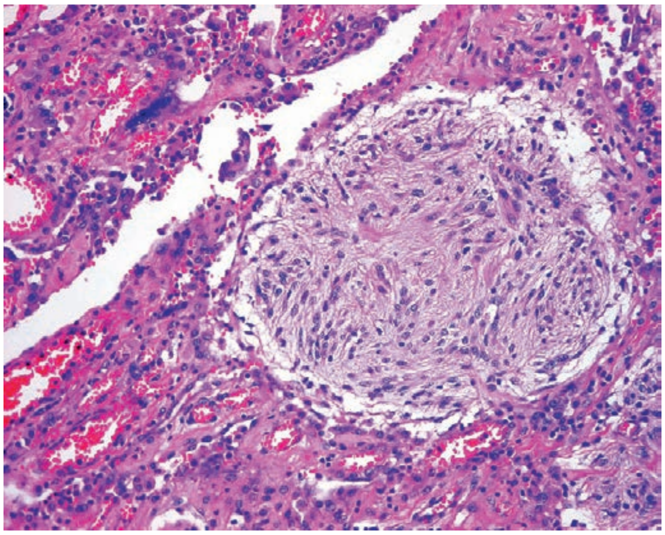

Figure 35.74 Peritoneal implant of mature glial tissue associated with an ovarian teratoma (so-called gliomatosis peritonei).

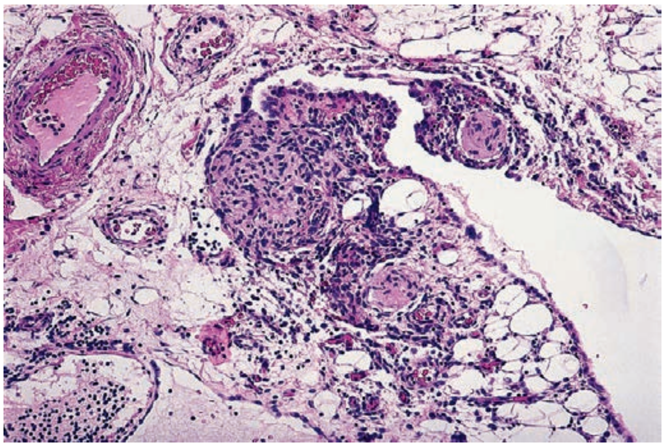

Figure 35.75 Peritoneal implants secondary to immature ovarian teratoma. When the appearance of the implants is immature, as shown here, the prognosis is more guarded than in gliomatosis peritonei (compare with Fig. 35.74).

"Somatic-type" Tumors Developing in Mature Cystic Teratoma

Emergence of a benign or a malignant neoplasm with somatic-type features is an uncommon event in mature cystic teratoma, occurring in approximately 2% of all cases.

The most common malignant change in cystic teratoma is squamous cell carcinoma (possibly arising from metaplastic columnar epithelium),[467] followed by carcinoid tumor and adenocarcinoma.[468–471] These ovarian squamous cell carcinomas typically present in the 5th or 6th decade, suggesting that transformation requires prolonged contact between the epithelium and the cyst contents. The prognosis of squamous cell carcinoma arising from a teratoma is guarded and these tumors are characterized by aggressive locally invasive growth.[469] Other types include malignant melanoma,[472,473] Paget disease,[474]sarcomas of various types, carcinosarcoma, glioblastoma multiforme,[475] central-type neurocytoma,[476] and neuroblastoma/PNET.[477,478] This malignant transformation is accompanied by complex chromosomal aberrations.[479] An interesting twist is the occurrence of mucinous borderline tumors and adenocarcinomas similar to appendiceal neoplasms and resulting in pseudomyxoma peritonei.[480–482] These mucinous tumors arising in association with teratoma have a complete intestinal immunophenotype, indistinguishable from that of colorectal neoplasms. In an elegant study by Kerr et al., they were able to demonstrate, by DNA typing, that these mucinous neoplasms associated with a teratoma are of germ cell origin, while those without a teratomatous component are of somatic origin.[201] The teratoma component may be inconspicuous or consist of a monodermal component such as a carcinoid tumor.

Benign tumors have also been described, such as blue nevus,[483,484] sebaceous adenoma,[485] sweat gland tumors,[486] glomus tumor,[487] epithelioid (histiocytoid) hemangioma,[488] and various types of pituitary adenoma.[489,490]

Epidermoid Cyst

The rare **epidermoid cyst** of the ovary possibly arises from epithelial cell nests, of the type encountered in Brenner tumors.[65] It is distinguished from mature cystic teratoma on thorough sampling by the absence of skin adnexa and other tissues. It is discussed here not only in the light of this differential diagnosis but also because of the distinct possibility that some of these lesions were mature cystic teratomas in which the skin adnexal components were either missed or absent.

Struma Ovarii

Struma ovarii is the expression of the dominant growth of thyroid tissue in a teratoma, sometimes to the exclusion of other components (Fig. 35.76).[491] Grossly, the mass has the color and consistency of thyroid tissue, but it is often cystic (Fig. 35.77). These cystic changes can be very prominent and obscure the diagnosis, and result in a misdiagnosis of serous cystadenoma.[492,493] The thyroid nature of the lesion has been fully documented with biologic and immunohistochemical studies for TTF-1 and thyroid hormones.[494] The tissue may show any of the pathologic changes seen in a normally placed gland, including diffuse or nodular hyperplasia (which may lead to hyperthyroidism[495]), thyroiditis, papillary carcinoma (including the follicular or microcarcinoma variants[496] and featuring either *RAS* or *BRAF* mutation),[497,498] follicular carcinoma (sometimes resulting in peritoneal spread, so-called peritoneal strumosis),[499,500] and malignant lymphoma.[494,501] Some of the carcinomas are extremely well differentiated,[498,499,502] whereas others have a predominantly solid or trabecular pattern.[493]

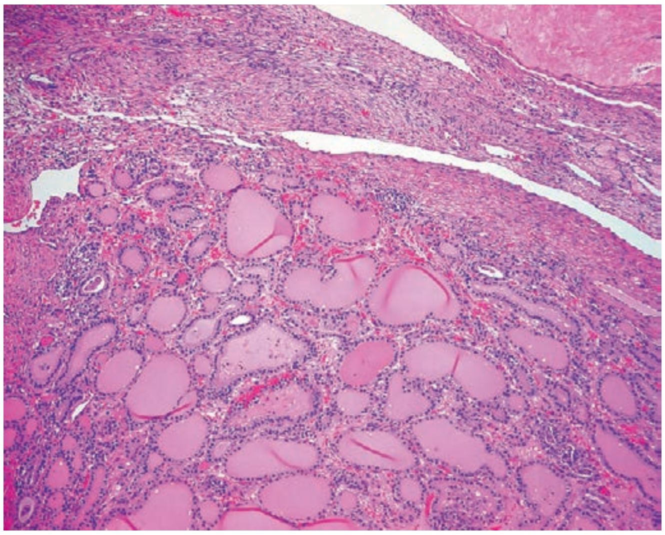

Figure 35.76 Struma Ovarii. The thyroid tissue, which has a microscopically unremarkable appearance, is sharply delimited from the ovarian stroma.

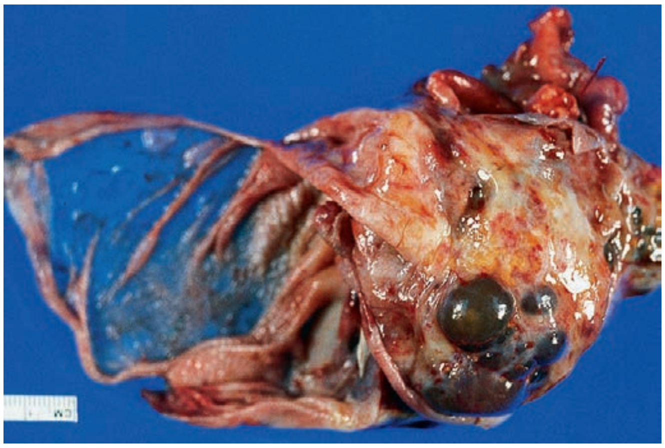

Figure 35.77 Gross Appearance of Struma Ovarii. The thyroid tissue is represented by the solid areas.

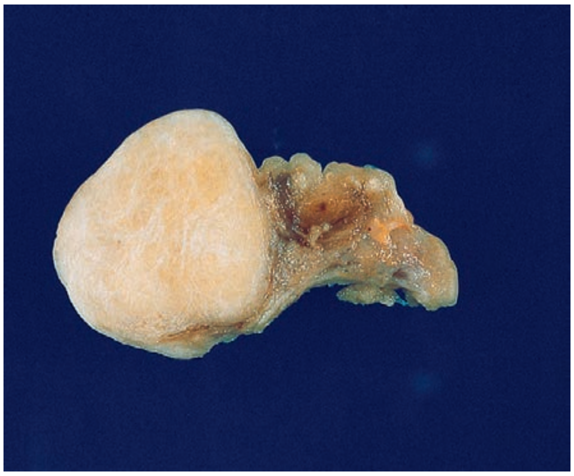

Figure 35.78 Cut surface of carcinoid tumor of ovary showing typical solid appearance and white to yellowish color.

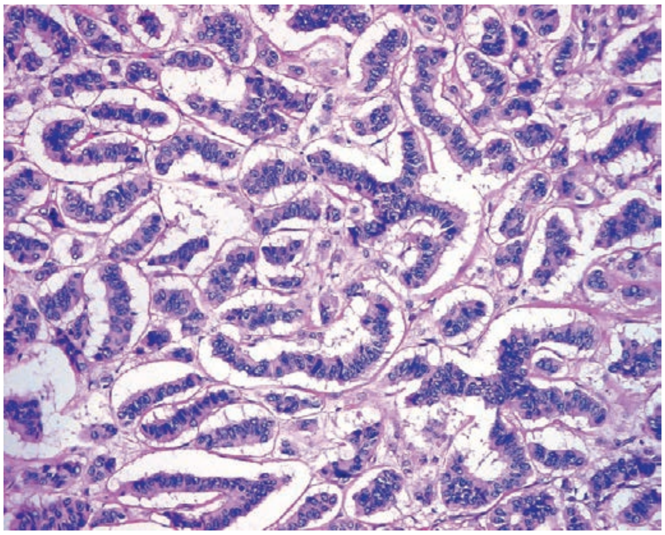

Figure 35.79 Primary Ovarian Carcinoid Tumor With a Trabecular Pattern of Growth. There is a close resemblance to carcinoid tumors of lung and rectum.

Struma ovarii can be seen combined with mucinous cystadenoma, Brenner tumor, or carcinoid tumor. The latter combination, known as strumal carcinoid, is discussed in the following section.

Carcinoid Tumor and Strumal Carcinoid

Carcinoid tumor can be seen in the ovary as a metastasis of a primary tumor located in the gastrointestinal tract or elsewhere,[503] as a component of adult cystic teratoma, or as a primary pure neoplasm of this organ. Approximately one-third of the latter are associated with the carcinoid syndrome, even in the absence of liver metastases[504]; the larger the tumor, the more likely that the carcinoid syndrome will develop. Some cases present with severe constipation, presumably because of secretion of peptide YY.[505] Small tumors arising in cystic teratomas are nearly always asymptomatic. The large majority of primary ovarian carcinoid tumors are unilateral, but in 16% of cases the contralateral ovary is involved by a cystic teratoma or a mucinous neoplasm.[506] In contrast, most metastatic carcinoid tumors to the ovary are bilateral and associated with peritoneal metastases. The prognosis in primary ovarian carcinoid tumors (whether pure or as a component of cystic teratoma) is very good, whereas metastatic carcinoids have a poor outcome.

Grossly, pure primary carcinoid tumors have a mean diameter of 10 cm; their external surface is smooth or bosselated, and the cut surface is predominantly solid, firm, tan to yellow, and homogeneous (Fig. 35.78). Microscopically, the appearance is similar to that of carcinoid tumors elsewhere, in that they recapitulate the various patterns of this well-differentiated neuroendocrine tumor as seen in various sites. Thus, there are tumors with an *insular* pattern of growth similar to those seen in the appendix and small bowel, tumors with a *trabecular* appearance similar to those seen in the rectum (Fig. 35.79), and tumors with a *mucinous* (goblet cell) appearance similar to those seen primarily in the appendix.[507–509] The similarities also apply to the occasional presence of pleomorphic forms,[510] to their histochemical features (argentaffinity or argyrophilia depending on the type), and to the consistent presence of neurosecretory granules at the electron microscopic level.[511]

Neuron-specific enolase (NSE), chromogranin, 5-HT, and a large variety of peptide hormones (including peptide YY) have been demonstrated immunohistochemically, particularly in tumors of the trabecular type.[505,512]

It is not possible to separate primary from metastatic carcinoid tumors on morphologic grounds; however, if the ovarian carcinoid is admixed with areas of teratoma, the chances are overwhelming that it is of primary origin. Conversely, tumors with goblet cell carcinoid-like features and signet ring patterns (traditionally known as goblet cell carcinoid tumors, see Chapter 16) are likely to be metastases from the appendix.[513] A potential pitfall should be mentioned here: primary ovarian carcinoid tumors and those metastatic from the gastrointestinal tract show identical immunoprofiles (e.g. expression of CDX2),[514] so immunohistochemistry is not helpful in distinguishing primary from metastatic carcinoid tumor.

Excision of a primary ovarian carcinoid of insular or trabecular type is usually curative. As in the appendix, the behavior of the mucinous type is more aggressive, particularly if the tumor contains a clear-cut carcinomatous component.[507]

Strumal carcinoid is an ovarian neoplasm combining the features of carcinoid tumor and struma ovarii (Fig. 35.80).[515] There was some question about the thyroidal nature of the latter element on the basis of ultrastructural studies, but the immunohistochemical demonstration of thyroglobulin and TTF-1,[516,517] and the occasional occurrence of thyroid-type papillary microcarcinomas[518] have settled the issue. The interesting suggestion has been made that the carcinoid-like component represents a medullary carcinoma arising from thyroid C cells,[519] but the morphologic appearance and immunohistochemical profile of the tumor are more akin to those of a trabecular carcinoid of hindgut derivation[520,521]; specifically, calcitonin and amyloid are only rarely demonstrable.[522] It is of interest that these tumors also exhibit immunoreactivity for prostatic acid phosphatase in the carcinoid component, as further evidence of their similarity to rectal (hindgut-type) carcinoids.[523] The occasional occurrence of severe constipation, presumably due to secretion of peptide YY,[511] and of carcinoid heart disease[524] also link it with pure ovarian carcinoid tumor. Exceptionally, the carcinoid component is of mucinous type.[525]

Other teratomatous elements are found in over 50% of the cases of strumal carcinoid.[504] This lesion has also been observed in association with multiple endocrine neoplasia type 2a.[526]

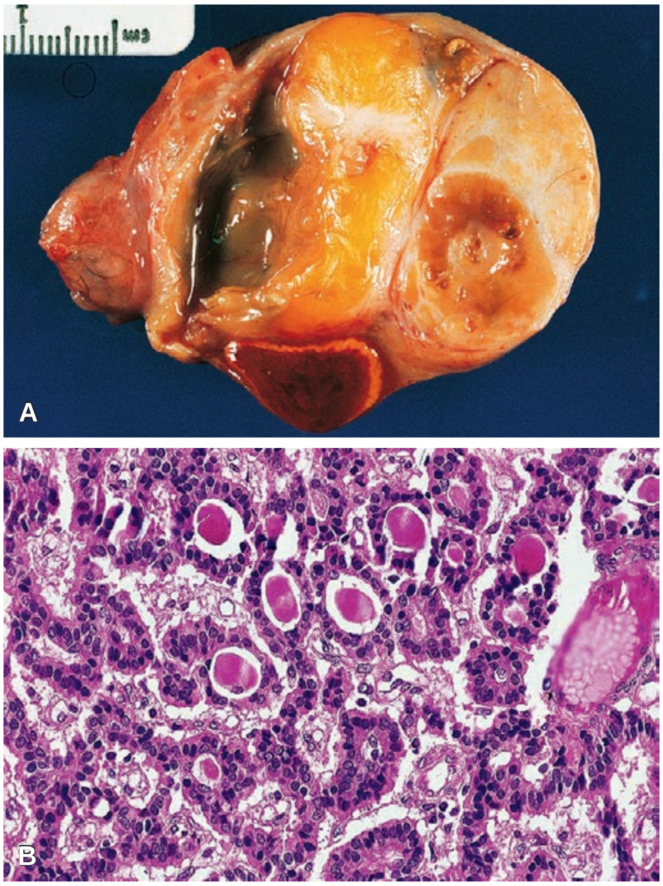

Figure 35.80 **A**, Gross appearance of strumal carcinoid showing a variegated appearance resulting from the admixture of carcinoid tumor and struma ovarii. **B**, Microscopic appearance, showing intimate admixture of thyroid follicles and carcinoid trabecula.

Sex Cord–Stromal Tumors

Sex cord–stromal tumors, which comprise approximately 5% of all ovarian neoplasms, are tumors that differentiate in the direction of sex cords and/or the specialized ovarian stroma.[527] This includes female-type cells (granulosa and theca cells), male-type cells (Sertoli and Leydig cells), and indifferent elements.[528,529] These various elements can occur in combination[530] and exhibit a wide range of differentiation, which often seems to recapitulate the patterns produced during embryogenesis of both the ovary and testis, as proposed many years ago by Gunnar Teilum.[531] Secondary changes, such as luteinization, may also develop. As a result, a wide array of tumor types may be seen, some of which do not fit easily into a rigid classification system. In general, a relationship exists between the morphologic appearance of the tumor and the presence and type of clinically evident hormonal activity.[532–534] However, there may be no demonstrable endocrine effects, and rare examples of hormonal effects opposite to those expected from the morphologic features also occur.[535,536]

Recently, a number of immunohistochemical markers have become available that are of considerable assistance in the identification of these tumors.[537,538] *Inhibin* has emerged as one of the most useful.[539] The α-subunit of the molecule seems to have a greater degree of specificity than the β-subunit.[540,541] It stains all types of sex cord–stromal tumors, the sex-cordlike elements of other gynecologic neoplasms, and most trophoblastic tumors.[542,543] It is also useful for the identification of steroid hormone-secreting cells in the non-neoplastic stroma component of epithelial, germ cell, and other types of ovarian tumor.[544] It has been reported to stain some carcinomas at other sites,[545] but this seems to be due at least in part to endogenous biotin, in older studies where avidin-biotin detection systems were used.[546] It should be also pointed out that negativity for inhibin does not rule out a diagnosis of sex cord–stromal tumor (following the general rule that a negative stain never rules out anything).

Molecules functionally related to inhibin that also stain sex cord–stromal tumors are activin (a molecule biochemically similar to inhibin but with an opposite function, and composed of two βA-subunits), müllerian inhibiting substance (anti-müllerian hormone), and relaxin-like factor.[537,547,548]

Calretinin is more sensitive but less specific than inhibin, in the sense that it often stains sex cord–stromal tumors that are inhibin negative, such as fibromas.[549–551] However, it also stains a good number of surface epithelial neoplasms.

Melan-A is consistently expressed in sex cord–stromal tumors and other types of steroid-producing cells, such as those of ovarian steroid cell tumor and adrenal cortical neoplasms.[552] Like calretinin, however, it lacks specificity as a marker of sex-cord stromal differentiation.

FOXL2 is a transcription factor, expressed in the nuclei of tumor cells; this can be an advantage in staining cells with scant cytoplasm (e.g. adult granulosa cell tumors and fibromas), where cytoplasmic stains such as inhibin may not be positive.[549] It is a very sensitive marker of sex cord-stromal tumors with the exception of Sertoli–Leydig cell tumors (only 50% stain) and steroid cell tumors (most are negative).

SF-1 (steroidogenic factor 1) is a sensitive sex cord–stromal marker.[553]

WT1, present in normal granulosa cells, is also expressed by a majority of ovarian sex cord–stromal tumors.[542]

Sex cord–stromal tumors of ovarian type are exceptionally encountered in extraovarian locations, such as the broad ligament.[554]

Granulosa Cell Tumor

Granulosa cell tumor is a sex cord–stromal ovarian neoplasm showing differentiation toward follicular granulosa cells. Two distinct types exist, known respectively as adult and juvenile.

Adult granulosa cell tumor is usually diagnosed during childbearing age, but it can occur after menopause and sometimes (despite its name) before puberty. Three-fourths of cases are associated with hyperestrinism; the excessive production of estrogens can lead to isosexual precocious puberty in children[555] and to metrorrhagia in adults, including postmenopausal patients.[556] Some of the cases are hormonally inactive at the clinical level, and a very few are androgenic.[557,558]

Grossly, adult granulosa cell tumors have a smooth, lobulated outline and a predominantly solid cut surface (Fig. 35.81). The color is usually gray, but it may be yellow in areas of luteinization (Fig. 35.82). Cysts filled with straw-colored or mucoid fluid may be present (Fig. 35.83). Sometimes the cysts are so prominent as to simulate grossly the appearance of a cystadenoma (Fig. 35.84). Interestingly, a disproportionate number of androgenic granulosa cell tumors are large and cystic, either unilocular or multilocular.[558,559] The microscopic appearance of granulosa cell tumors is extremely variable, even within the same neoplasm. Patterns of growth include microfollicular (with Call–Exner bodies), macrofollicular, trabecular, insular, watered-silk, solid, pseudopapillary, and diffuse (sarcomatoid) (Fig. 35.85).[560,561] A theca cell component may also be present. Focal luteinization of either the granulosa or the theca cell component may occur[562]; it is particularly prominent in those tumors associated with pregnancy, together with edema and disorderly arrangement.[563] An important diagnostic feature is the presence of folds or grooves in the nuclei, resulting in a "coffee-bean" appearance (Fig. 35.86). Occasionally, bizarre nuclei and multinucleated giant cells (some of the "floret" type) are seen; this change is not a sign of malignancy, but rather of a degenerative nature.[564] Rare cases of granulosa cell tumor have been reported exhibiting hepatocytic differentiation[565,566] and others are associated with mucinous cystadenoma.[567]

Consistent immunohistochemical markers of granulosa cell tumors include vimentin, FOXL2, and SF-1 (see preceding section; Fig. 35.87).[549,556,568–571] Inhibin expression may be weak or absent in

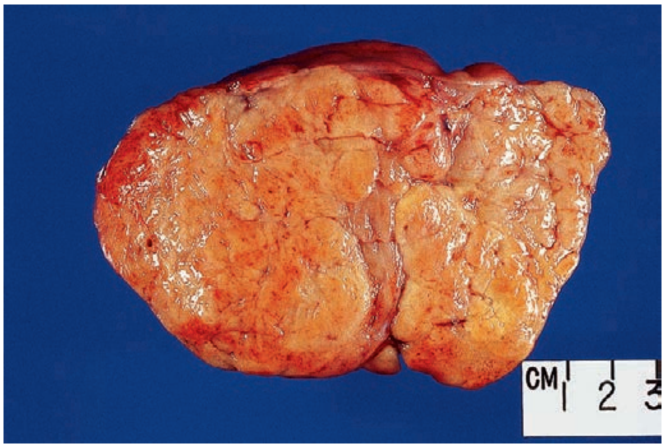

Figure 35.81 Adult granulosa cell tumor with solid cut surface.

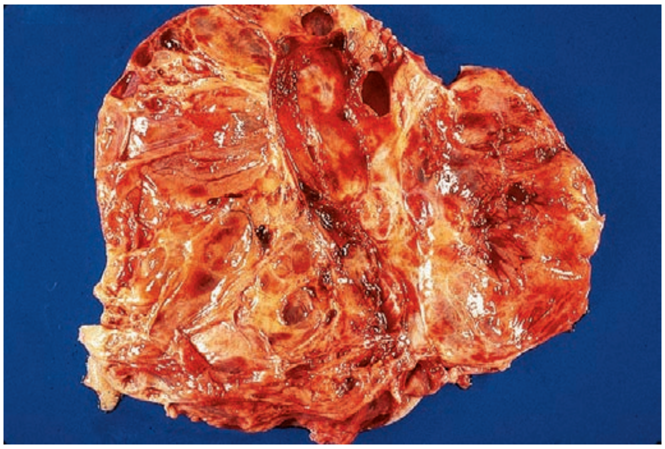

Figure 35.82 Adult granulosa cell tumor showing admixture of solid and cystic areas.

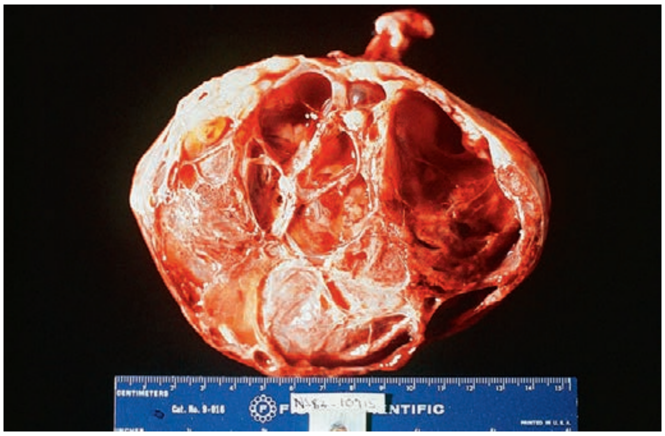

Figure 35.83 Predominantly cystic adult granulosa cell tumor.

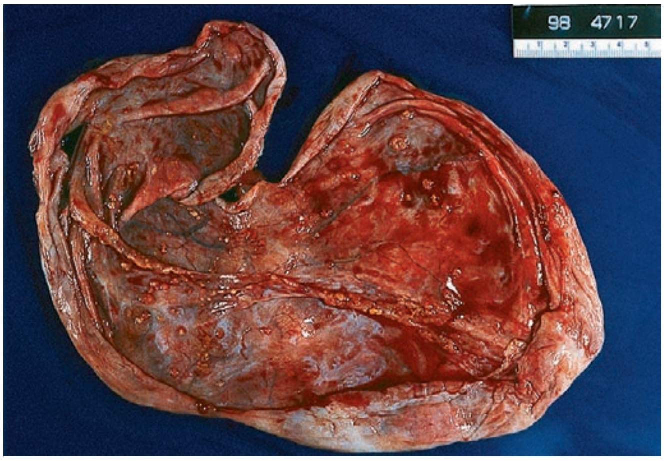

Figure 35.84 Adult granulosa cell tumor with an entirely cystic gross appearance.

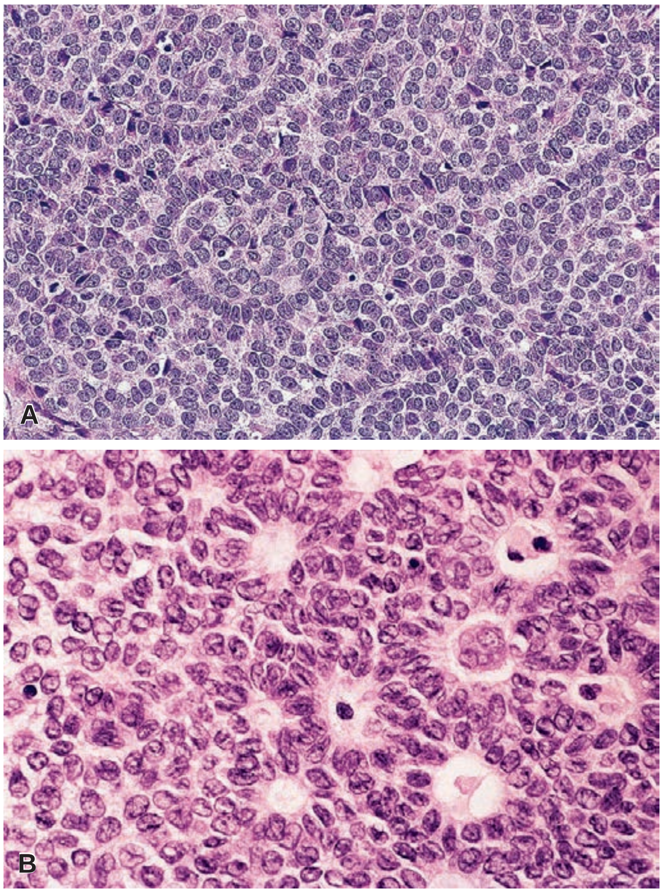

Figure 35.85 **A** and **B,** Microscopic appearance of adult granulosa cell tumor. Call–Exner bodies are seen in **B**.

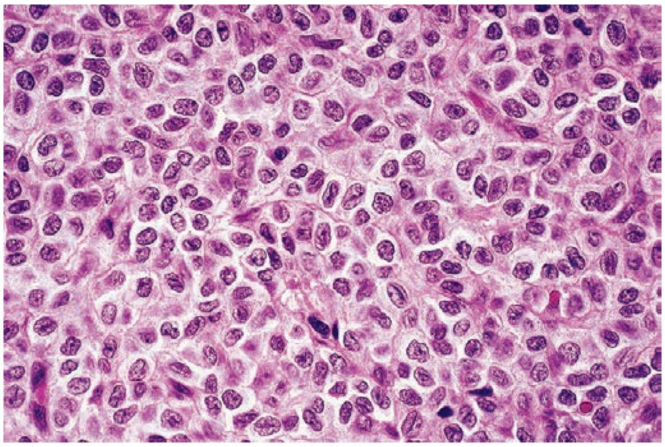

Figure 35.86 Coffee-bean nuclei in adult granulosa cell tumor.

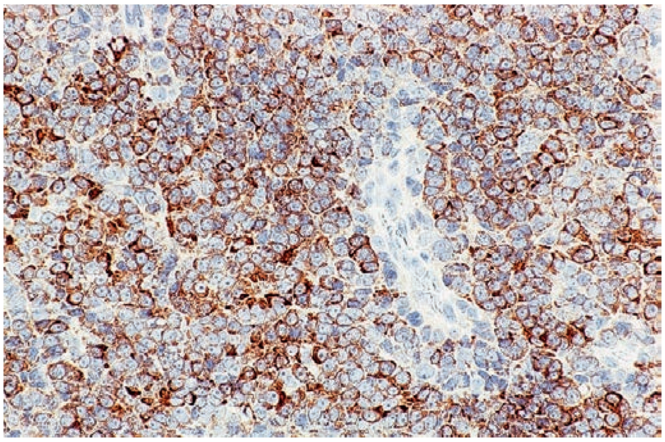

Figure 35.87 Strong immunoreactivity for inhibin in adult granulosa cell tumor.

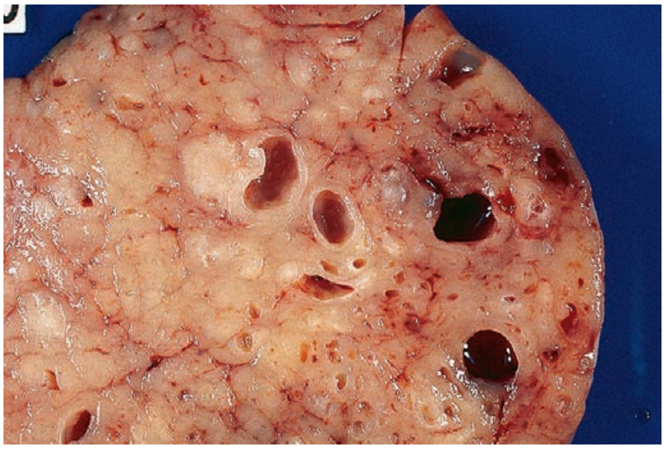

Figure 35.88 Gross appearance of juvenile granulosa cell tumor.

tumors where the cells have very scant cytoplasm, and this is a frequent source of diagnostic confusion. Keratin expression is present in one-third to one-half of cases; it has a typical dot-like distribution and consists mainly of CK8 and CK18 types.[572] Approximately 50% of cases are reactive for S-100 protein, whereas none are immunoreactive for EMA.[573] Estrogen and progesterone receptors are usually expressed.[574] The peptide hormone inhibin and follicle regulatory proteins, two substances normally produced by ovarian granulosa cells, have been found to be elevated in the serum of patients with granulosa cell tumor.[575] Curiously, granulosa cell tumors have also been found to be often immunoreactive for CD99, a marker associated with Ewing sarcoma.[568]

Recently, it has been shown that almost all cases of adult granulosa cell tumor show somatic mutation in the *FOXL2* gene (402C→G),[567,576,577] and this has emerged as a useful diagnostic marker. Except for occasional well- or moderately differentiated Sertoli–Leydig cell tumors, *FOXL2* mutation is specific for adult granulosa cell tumor. Mutational status need not be assessed in a typical adult granulosa cell tumor, but in diagnostically challenging cases, *FOXL2* mutation testing can be invaluable in confirming/excluding adult granulosa cell tumor.[577]

Juvenile granulosa cell tumor is diagnosed in nearly 80% of cases during the first two decades of life, most patients presenting with isosexual precocity (Fig. 35.88). A few cases have been associated with enchondromatosis (Ollier disease)[578] or Maffucci syndrome.[579] Typical morphologic features of this subtype include diffuse or macrofollicular patterns of growth (the former predominating), mucin-positive intrafollicular secretion, larger tumor cells with extensive luteinization, paucity of nuclear grooves, presence of a thecal component, nuclear atypia, and variable but often high mitotic activity (Fig. 35.89).[580,581] Like their adult counterpart, they may exhibit pseudopapillary features.[560] They also show consistent trisomy for chromosome 12.[582]

The differential diagnosis of granulosa cell tumor (particularly of the adult variety) includes poorly differentiated (predominantly

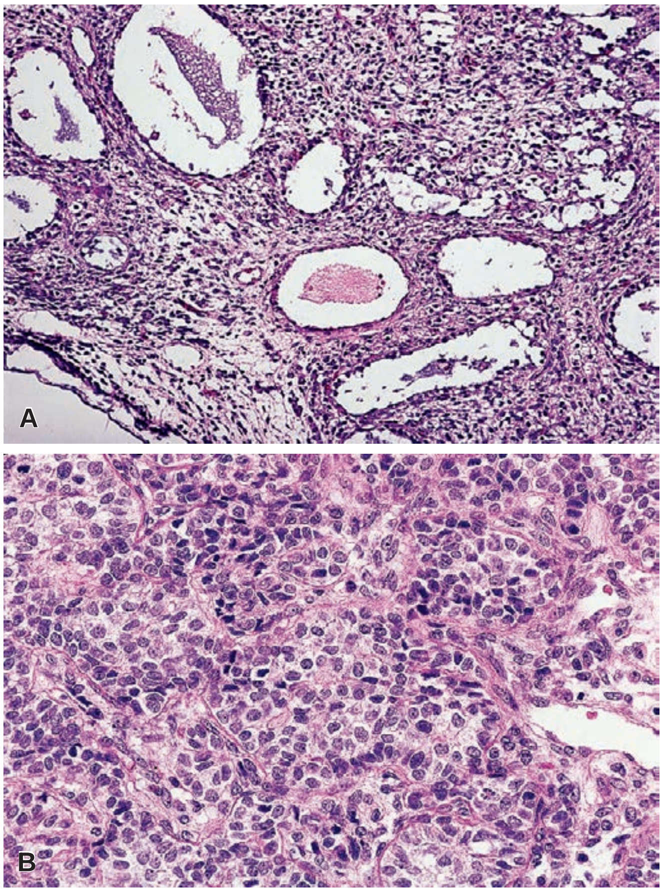

Figure 35.89 **Juvenile Granulosa Cell Tumor.** The follicle-like spaces seen on low-power examination **(A)** are a common feature of this neoplasm. On high power **(B)** the tumor cells are seen to lack the coffee bean nuclei seen in the adult type.

solid) carcinoma of surface epithelial origin, carcinoid tumor, and the rare tumors of endometrial stromal type.[542] The nuclear features are of crucial importance in this regard. Some early series describing a poor prognosis for granulosa cell tumors are contaminated with solid-pattern ovarian carcinomas (i.e. tumors of epithelial rather than sex-cord origin).[583] Strong and widespread positivity for keratin should point toward the direction of carcinoma in a controversial case, especially if this positivity is diffuse cytoplasmic rather than dot-like. The differential diagnosis also includes the *ovarian granulosa cell proliferations of pregnancy*; this change is usually microscopic, multiple, and associated with atretic follicles.[584]

The prognosis of granulosa cell tumors is largely dependent on the clinical stage and resectability of the tumor. Adult granulosa cell tumors are indolent, and the prognosis is little different from age matched controls[583]; however, pelvic or upper abdominal metastases do occur, especially in cases with intraoperative tumor rupture. Importantly, these clinical relapses may occur 10 or even 20 years after initial surgery. Juvenile granulosa cell tumors are also associated with a favorable prognosis, especially when confined to the ovary at diagnosis, as is true in most patients.

Thecoma, Fibroma, and Related Tumors

Fibroma and thecoma are closely related tumors, but distinction between them is possible in most cases (although some recommend a diagnosis of *fibrothecoma* for all tumors in this category).

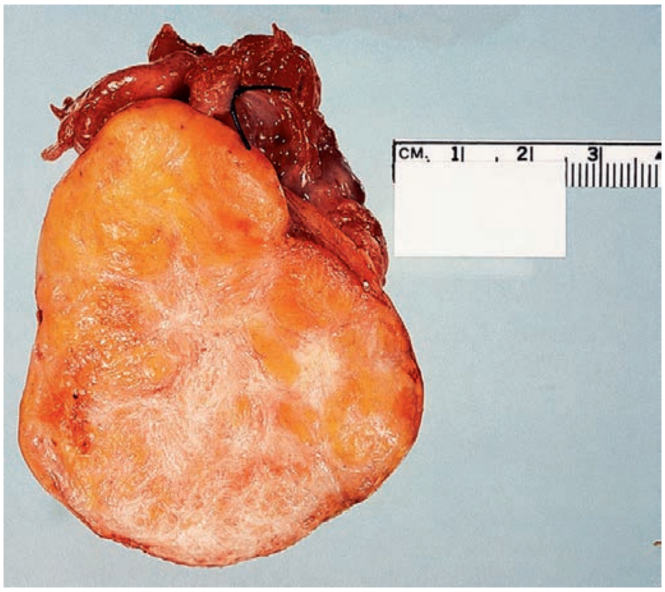

Figure 35.90 Cut surface of thecoma showing a predominance of yellow areas alternating with whitish foci.

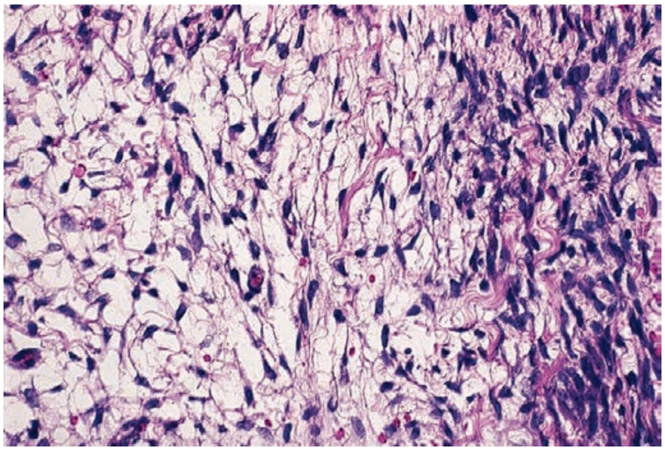

Figure 35.91 Bland microscopic appearance of thecoma, with some variability in cellularity.

Thecoma presents after menopause in 65% of patients. It is usually unilateral and varies considerably in size. It has a well-defined capsule and a firm consistency. The cut surface is largely or entirely solid, but cysts may be present. It has a yellow color, an important feature in the differential diagnosis with fibroma (Fig. 35.90). Microscopically, it is composed of fascicles of spindle cells with ill-defined borders, centrally placed nuclei, and a moderate amount of pale grayish-pink cytoplasm (Fig. 35.91). The intervening tissue may show considerable collagen deposition and focal hyaline plaque formation. The degree of cellularity varies considerably. Some tumors in young women are heavily calcified.[585]

With oil red O, the cells of thecoma show abundant intracytoplasmic neutral fat, and silver stains usually demonstrate reticulin fibers surrounding individual cells (as opposed to granulosa cell tumor, in which the reticulin surrounds clusters of cells). The differential diagnosis with a luteinized adult granulosa cell tumor can be challenging; *FOXL2* mutational analysis can be of use in such cases, with the presence of a mutation supporting the diagnosis of adult granulosa cell tumor.[577]

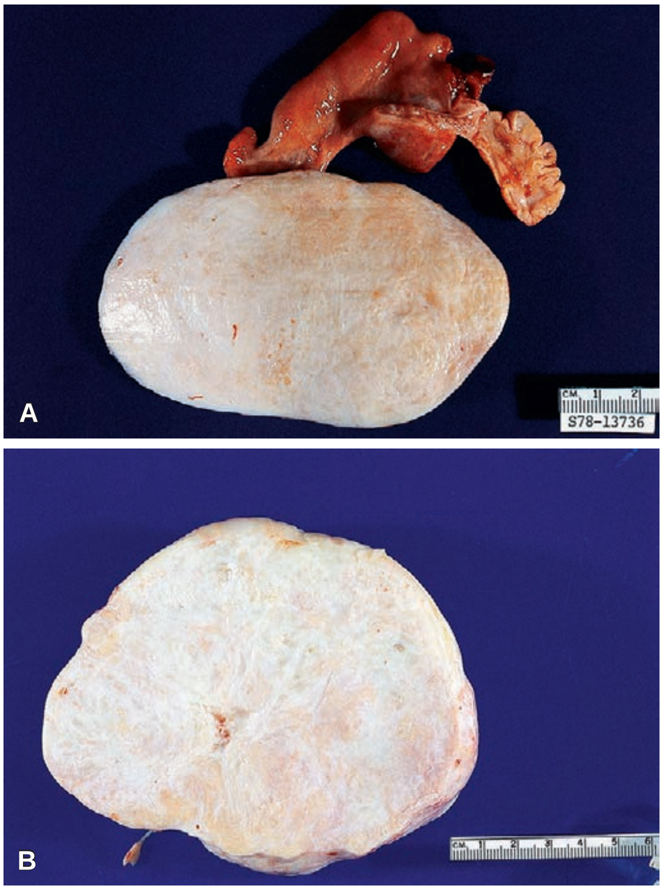

Figure 35.92 **A** and **B,** Outer aspect and cut surface of ovarian fibroma. The white color contrasts with the yellow hue of thecoma (compare with Fig. 35.90).

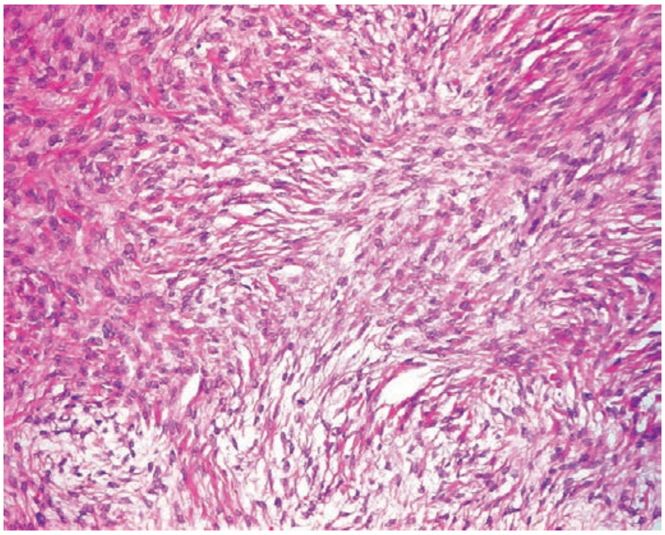

Figure 35.93 Ovarian fibroma showing, bland nuclear features, and a suggestion of a storiform pattern of growth.

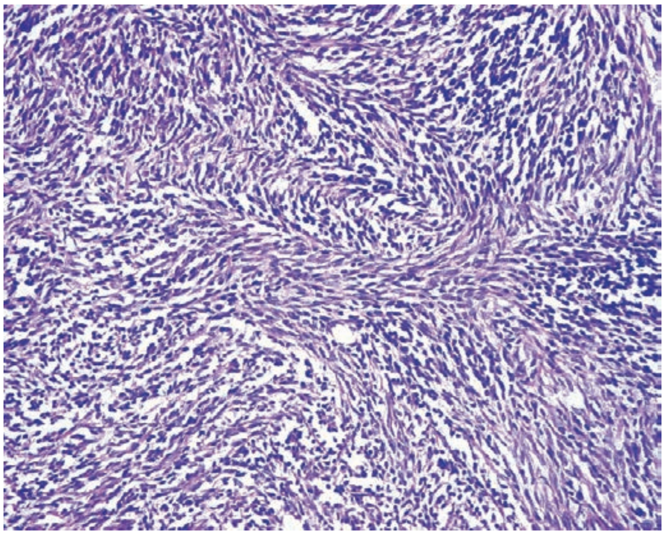

Figure 35.94 Cellular fibroma. The tumor is hypercellular, but pleomorphism and mitotic activity are minimal.

Thecomas may be associated with prominent stromal hyperplasia, particularly in postmenopausal patients. Thecomas are typically associated with estrogenic manifestations, although some (particularly those containing steroid cells, as just indicated) may be androgenic. They are nearly always benign, but a few malignant examples have been documented.[586] Some ovarian tumors with the overall appearance of thecoma with luteinized stromal cells have been found to be associated with a peculiar form of *sclerosing peritonitis;* in this context they have been referred to as stromal luteomas.[587–589]

Fibromas are common ovarian tumors, usually unilateral, which occur almost invariably after puberty.[590] They are solid, lobulated, firm, uniformly white, and usually not accompanied by adhesions (Fig. 35.92). The average diameter is 6 cm. Myxoid or edematous changes may be seen, sometimes resulting in cystic degeneration. Grossly, fibromas may have an appearance similar to thecoma, Brenner tumor, and Krukenberg tumor.

Microscopically, fibromas are composed of closely packed spindle stromal cells arranged in a "feather-stitched" or storiform pattern (Fig. 35.93). Hyaline bands, edema, and hyaline globules may be present.[591] Some fibromas occur in young women with the basal cell nevus (Gorlin) syndrome; these are calcified, usually bilateral, and often multinodular.[592] Fibromas exhibiting a high degree of cellularity can be referred to as *cellular fibromas* (Fig. 35.94). Some cellular fibromas can have conspicuous mitotic activity, and these may be diagnosed as *mitotically active cellular fibroma*, but the diagnosis of *fibrosarcoma*[593] should be reserved for tumors with moderate to severe atypia, with or without necrosis (Fig. 35.95).[594] Differences between ovarian fibroma and fibrosarcoma have also been described at the DNA ploidy, genetic, and cell proliferation levels.[595]

Some otherwise typical fibromas have a minor component of sex cord elements.[596]

Cytogenetically, both thecomas and fibromas have been found to exhibit trisomy of chromosome 12 in a minority of the tumor cells.[597,598] Loss of heterozygosity at both the *PTCH* gene (implicated in Gorlin syndrome) and the *STK11* gene (implicated in Peutz–Jeghers syndrome) is relatively frequent in cellular fibromas.[599]

Fibromas are distinguished from thecoma by their gross appearance (white rather than yellow), the absence of significant cytoplasm in the tumor cells, and the lack of evidence of hormone production (e.g. endometrial hyperplasia or carcinoma).

Ovarian fibroma (especially if large) can be associated with ascites, sometimes in combination with right-sided pleural effusion (Meigs syndrome).[600,601] This may lead to a mistaken impression of inoperable ovarian neoplasm, but removal of the tumor leads to the disappearance of these manifestations. The mechanism for the pleural effusion

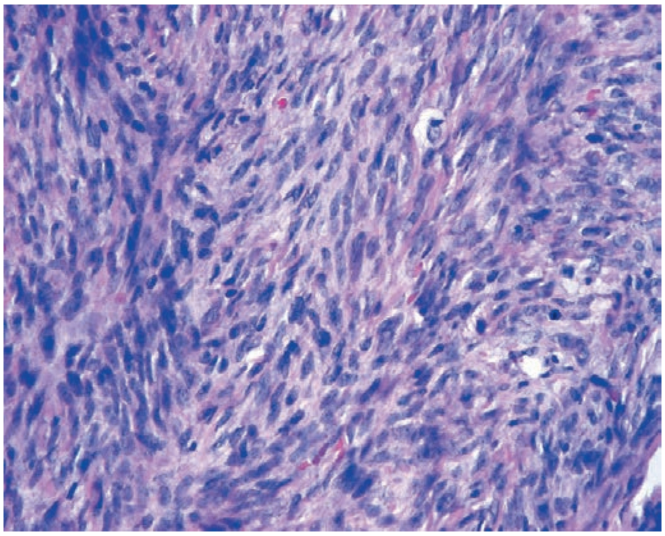

Figure 35.95 **Fibrosarcoma of Ovary.** Hypercellularity, nuclear hyperchromasia, and brisk mitotic activity are present. The latter is the most important feature in the differential diagnosis with cellular fibroma.

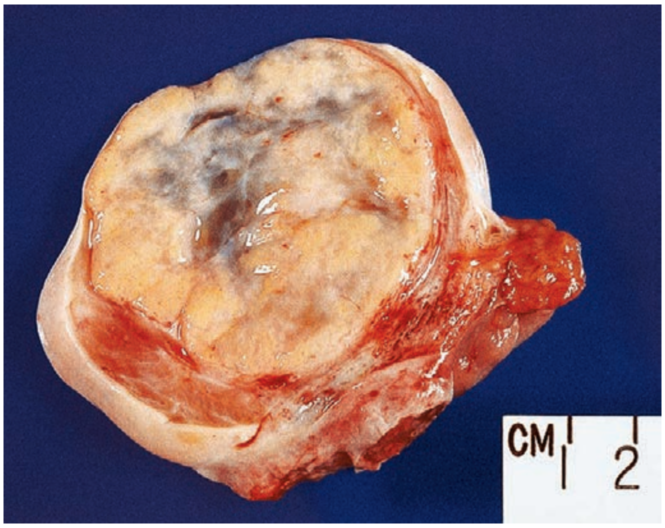

Figure 35.96 Multinodular quality of cut surface of sclerosing stromal tumor.

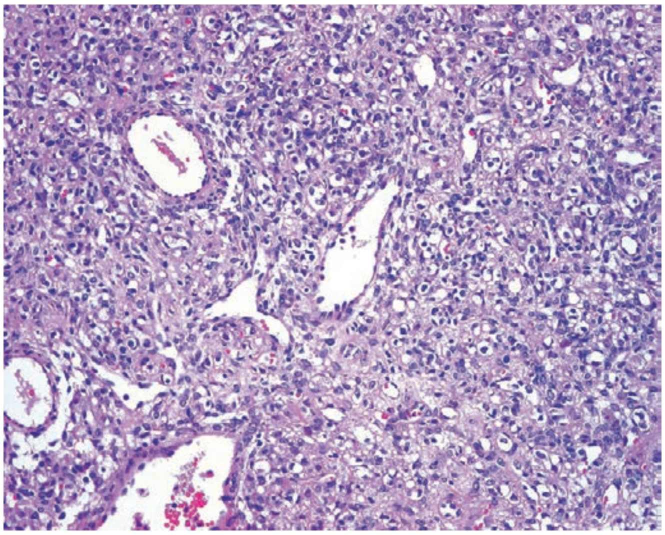

Figure 35.97 **Sclerosing Stromal Tumor of Ovary.** The hemangiopericytoma-like foci and the alternation of hypocellular and hypercellular areas are important diagnostic clues.

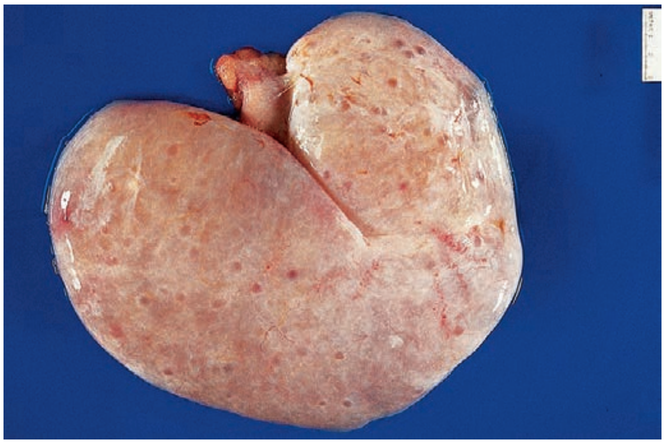

Figure 35.98 Bulging cut surface of ovary involved by massive edema.

is said to be related to intrathoracic negative pressure and transdiaphragmatic passage of fluid through peritoneal "pores" or lymphatics. Meigs syndrome can also occur in association with other ovarian tumors.[602]

Fibromas are benign, and oophorectomy is curative. However, cellular fibromas may recur or be associated with peritoneal implants.[593]

Sclerosing stromal tumor is a benign ovarian neoplasm that shares many features with fibroma and thecoma. However, it occurs in a younger age group, has a less homogeneous gross appearance (Fig. 35.96), and is characterized microscopically by a lobular pattern of growth, interlobular fibrosis, marked vascularity, and the presence of a dual cell population: collagen-producing spindle cells and lipid-containing round or oval cells (Fig. 35.97). Some of the latter may have a signet ring appearance and thus simulate a Krukenberg tumor.[603] Endocrine manifestations are rarely present.[604] The tumor cells are immunoreactive for smooth muscle actin and sometimes for desmin.[605,606] Cytogenetically, this tumor shares the tendency for trisomy 12 that is also a feature of fibromas and thecomas.[607]

Massive edema of the ovary is probably not a neoplasm but is a tumorlike condition discussed here because of its gross similarities with fibroma. Most patients present with pain, abdominal mass, and/or menstrual irregularities; virilization, precocious puberty, and Meigs syndrome have also been described.[608,609] Partial torsion of the meso-ovarium with interference in the venous and lymphatic drainage has been suggested as the pathogenetic mechanism.[609] The cut surface has been described as watery (Fig. 35.98). Microscopically, there is marked edema of the stroma surrounding follicles and other structures (Fig. 35.99).[610] Clusters of luteinized cells are often present.[611] The presence of follicles and other normal ovarian structures distinguishes massive edema and fibromatosis from fibroma.

Fibromatosis is the term proposed by Young and Scully[612] for a disorder that they proposed to be related to massive edema. The patients usually present because of menstrual irregularities. Grossly, the ovaries show a firm, white, cut surface. Microscopically, a diffuse proliferation of spindle cells separated by dense collagen is seen surrounding normal follicular structures. Luteinized cells may be

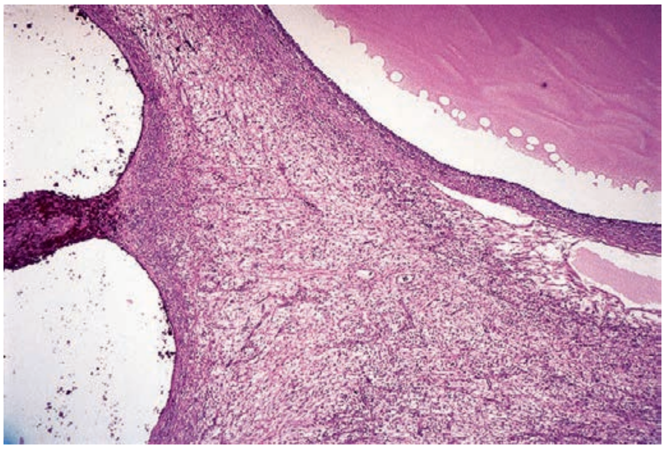

Figure 35.99 Massive edema of ovary typically surrounding dilated follicles.

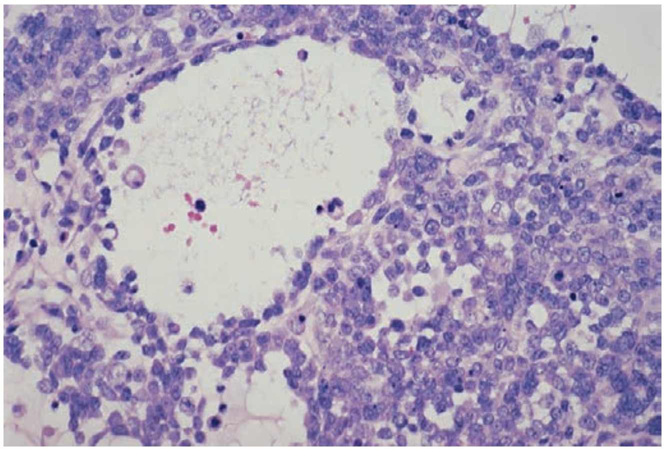

Figure 35.101 **Small Cell Carcinoma, Hypercalcemic Type.** The presence of follicle-like formations is an important diagnostic feature.

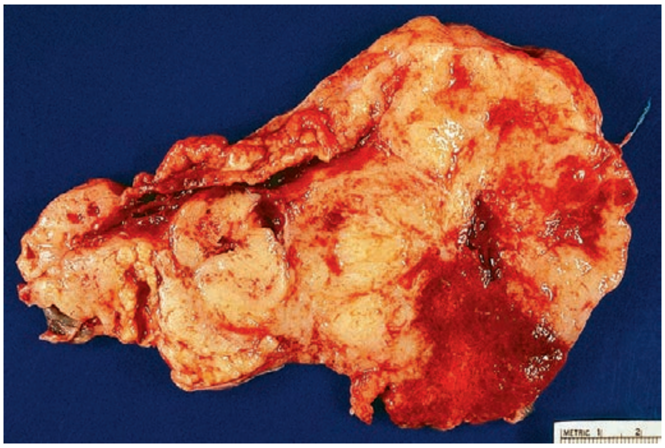

Figure 35.100 Solid cut surface with hemorrhagic foci in ovarian small cell carcinoma of hypercalcemic type.

present. The fact that some cases of massive ovarian edema are accompanied by small cellular foci of fibromatosis lends support to their interpretation. The term *fibromatosis*, although descriptively correct, should not be equated with the similarly named lesion of soft tissues (i.e. desmoid tumor), which under exceptional circumstances can involve the ovary.[613]

Myxoma of ovary presents as a solid and cystic mass, some of the cysts being occasionally filled with blood. Microscopically, scattered cells with fibroblastic/myofibroblastic features are seen in a well-vascularized myxoid background.[614,615] Some authors regard this as a distinct type of ovarian neoplasm, whereas others view it as part of the spectrum of differentiation in the fibrothecoma group.[616,617]

Small Cell Carcinoma of Hypercalcemic Type

Small cell carcinoma of hypercalcemic type is a high-grade ovarian malignancy that may be confused with granulosa cell tumor.[618–620] It occurs in young females (average age, 23 years) and is often bilateral. Familial cases have been reported.[621] The tumor is associated with hypercalcemia in up to two-thirds of cases, which disappears following removal of the tumor.[622] Grossly, the tumor is large and solid, with areas of necrosis and hemorrhage (Fig. 35.100). Microscopically, a diffuse proliferation of small, closely packed cells of carcinomatous appearance with scant cytoplasm and small nuclei is seen (Fig. 35.101). Clusters of larger and more pleomorphic rhabdoid cells are present in approximately half of cases. Cytoplasmic hyaline globules may also be seen. Tumors containing a large number of these larger cells have been referred to, tongue-in-cheek, as the "large cell variant" of small cell carcinoma. There may also be islands, cords, trabeculae, mucinous glands, and *follicle-like structures*. The latter are an important clue to the diagnosis.

The tumor cells usually express keratin, vimentin, EMA, and WT1 but not S-100 protein, chromogranin, inhibin, CD117, or OCT4.[623,624] The genetic basis of these tumors, whether sporadic or familial, has recently been elucidated[625–628]; most have mutations in the *SMARCA4* gene, which encodes the BRG1 protein, a component of the SWI/SNF chromatin remodeling complex. Loss of expression of both BRG1 and BRM (another SWI/SNF protein encoded by the *SMARCA2* gene) in an ovarian tumor appears to be completely specific for small cell carcinoma of hypercalcemic type.[629] The prognosis is very poor. The histogenesis remains obscure, but the occasional association with a germ cell tumor (mature or immature teratoma, or yolk sac tumor) has led to suggestions that it is a primitive germ cell tumor. The differential diagnosis of small cell carcinoma of hypercalcemic type includes **pulmonary-type small cell carcinoma,** which resembles the homonymous lung tumor (Fig. 35.102).[630] It may be pure or associated with endometrioid carcinoma or other patterns. Immunohistochemically, there is reactivity for keratin, EMA, NSE, and (rarely) for chromogranin and Leu7 (CD57). The prognosis is poor. They occur in older patients than small cell carcinoma of hypercalcemic type and are thought to represent dedifferentiation in an epithelial malignancy.

Sertoli–Leydig Cell Tumor

As the name indicates, Sertoli–Leydig cell tumors are composed of a mixture in variable proportions of cells morphologically resembling male Sertoli and Leydig cells; the Sertoli cell elements predominate with a variable, often inconspicuous Leydig cell component. This term replaces the old designations arrhenoblastoma and androblastoma and should be regarded as synonymous with Sertoli–stromal cell tumor. Pure Sertoli cell tumors are also included in this group, but pure Leydig cell tumors are included with the steroid cell tumors.[631] The interesting point has been made that the only neoplastic component of this tumor may be represented by the Sertoli cells, as the Leydig cell component has been shown to be polyclonal, in at least some cases.[632,633]

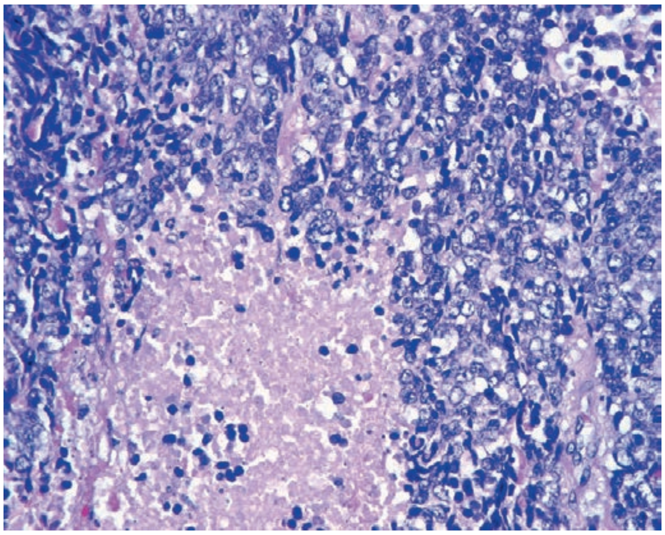

Figure 35.102 **Small Cell Carcinoma of Pulmonary Type.** The sharply outlined foci of necrosis are a common feature of this tumor, which has a microscopic appearance very similar to its pulmonary counterpart.

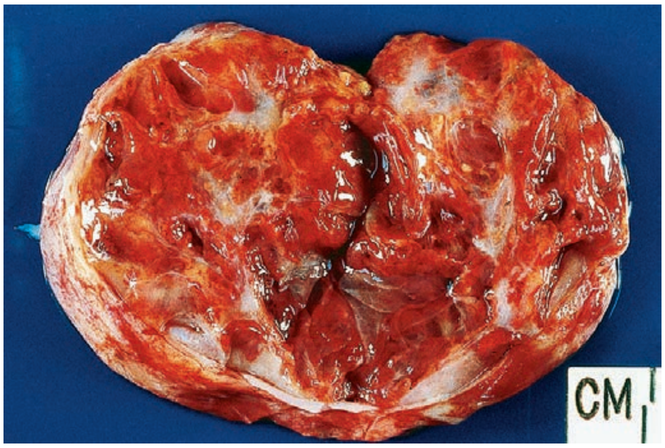

Figure 35.103 Variegated appearance of cut surface of ovarian Sertoli–Leydig cell tumor.

Sertoli–Leydig cell tumors are rare, comprising less than 0.1% of ovarian neoplasms. Grossly they are predominantly solid, but cystic areas may also be present (Fig. 35.103).

The microscopic pattern is extremely variable. Several major patterns have been described, which may coexist in the same tumor:

1. *Well differentiated* (11%). Composed of tubules lined by Sertoli-like cells separated by variable numbers of Leydig-like cells (Fig. 35.104).[634] Sometimes those tubules have a hollow "pseudoendometrioid" appearance, the tumor thus simulating a borderline or malignant endometrioid neoplasm.[635] The opposite phenomenon, endometrioid adenocarcinoma simulating Sertoli–Leydig cell tumor, also occurs (and is more common), immunohistochemical evaluation being sometimes necessary to arrive at a correct diagnosis.[636]
2. *Moderately differentiated (intermediate grade)* (54%). Characterized by the formation of cords, sheets, and aggregates of Sertoli-like cells, separated by spindle stromal cells and recognizable Leydig cells (Fig. 35.105).
3. *Poorly differentiated (sarcomatoid; undifferentiated)* (13%). Composed of masses of spindle-shaped cells arranged in a "sarcomatoid" pattern (Fig. 35.106).

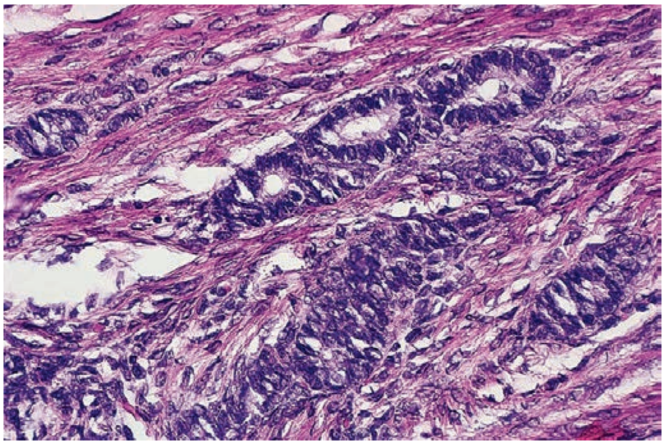

Figure 35.104 Well-differentiated Sertoli–Leydig cell tumor.

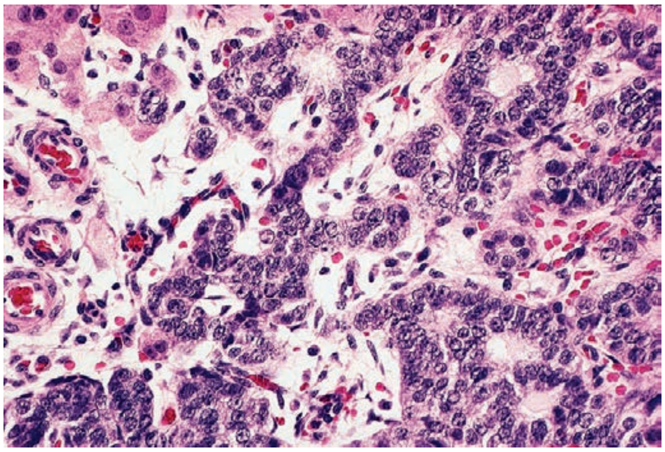

Figure 35.105 Moderately differentiated Sertoli–Leydig cell tumor.

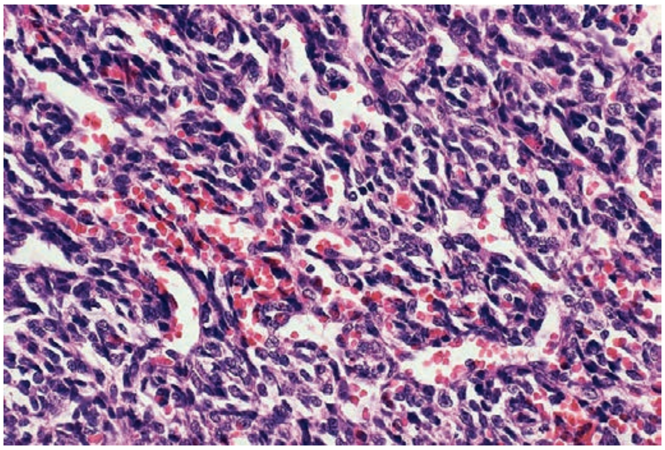

Figure 35.106 Poorly differentiated Sertoli–Leydig cell tumor.

4. *Pure Sertoli cell tumors.* Essentially identical to well-differentiated Sertoli–Leydig cell tumors but lacking Leydig cells and primitive stromal elements.[637,638] Abundant lipid may be present in the cytoplasm. The microscopic pattern can be tubular or follicle-like.[639] Amyloid-like material can be present, and cytoplasmic crystalline structures have been found by electron microscopy.[640] Some Sertoli cell tumors are composed of cells with oxyphilic cytoplasm.[641]

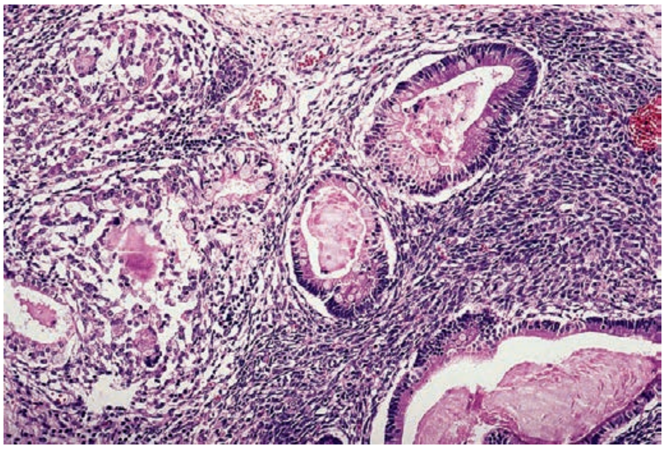

Figure 35.107 Sertoli–Leydig cell tumor with heterologous elements represented by well-differentiated mucin-secreting glands.

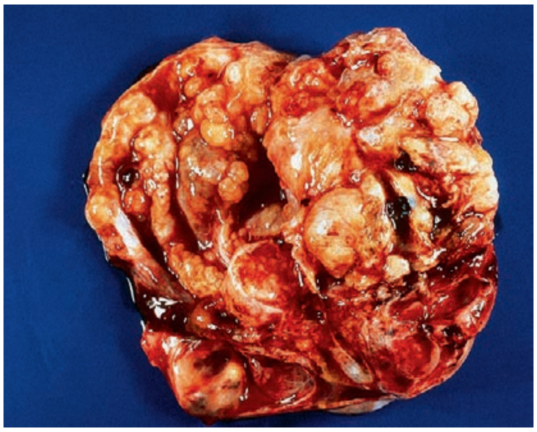

Figure 35.108 Gross appearance of Sertoli–Leydig cell tumor of the retiform variant.

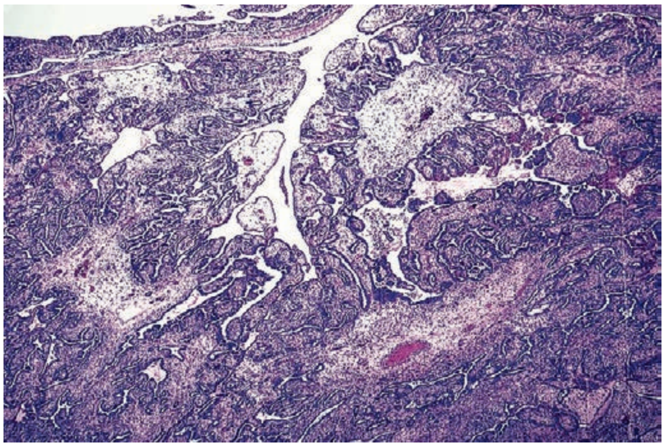

Figure 35.109 Retiform variant of Sertoli–Leydig cell tumor as seen on low-power examination. The retiform areas are represented by the micropapillary foci.

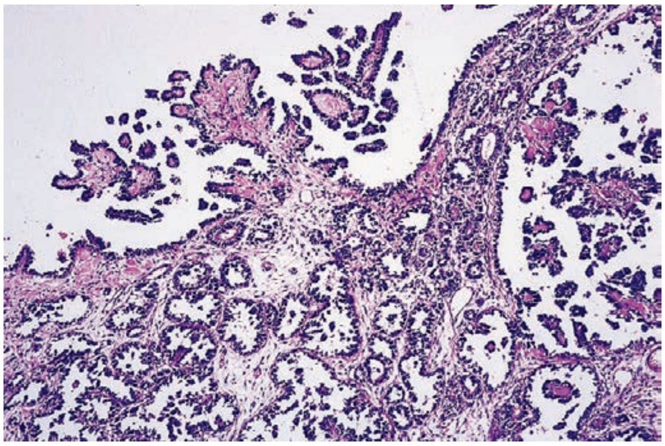

Figure 35.110 When the retiform type of Sertoli–Leydig cell tumor is made up predominantly or exclusively of retiform elements without conventional foci of Sertoli–Leydig cells, as seen here, the diagnosis can be easily missed.

5. *With heterologous elements* (22%). Rare cases are associated with tissues such as mucinous epithelium of gastrointestinal type, liver,[642] skeletal muscle, or cartilage (Fig. 35.107).[643,644] The epithelial component of this neoplasm contains a variety of endocrine cells[645] and can give rise to microscopic carcinoid tumors.[576,646]
6. *Retiform* (15%). In this category, typical elements of Sertoli–Leydig cell tumors coexist with formations resembling the rete of the ovary or testis (Figs. 35.108 and 35.109). These appear as irregular cleft-like spaces lined by low cuboidal cells; blunt papillae with hyalinized or edematous cores are often present. Sometimes the retiform formations predominate almost to the exclusion of the Sertoli–Leydig cell component (Fig. 35.110).[647,648] In other instances there is a hepatocytic component in the tumor, which may be difficult to distinguish from Leydig cells without immunostains.[649]

As in the case of granulosa cell tumor, the cells of a few Sertoli–Leydig cell tumors may contain bizarre and/or multiple nuclei, a change of no apparent prognostic significance.[579]

Immunohistochemically, testosterone and estradiol are found in both Sertoli and Leydig cells and less frequently in primitive stromal cells.[650] The areas of Sertoli cell differentiation stain for keratin and Sox-9 (but not for EMA, PLAP, CEA, or S-100 protein).[651] Positivity for inhibin, calretinin, and WT1 is seen in most tumors.[652,653]

Mutations in *DICER1*, which encodes an endoribonuclease involved in miRNA processing, are found in most Sertoli–Leydig cell tumors[654]; mutations are associated with young age at diagnosis, as well as higher-grade, heterologous elements, or retiform pattern. The *DICER1* mutations may be germline, in which case there is a hereditary predisposition not just to Sertoli–Leydig cell tumor but also pleuropulmonary blastoma and embryonal rhabdomyosarcoma.[655] A small number of low-grade Sertoli cell or Sertoli–Leydig cell tumors harbor a somatic FOXL2 mutation identical to that seen in 95% of adult granulosa cell tumors; these tumors are typically in patients who are older than the usual age of patients with Sertoli–Leydig cell tumor (i.e. postmenopausal), and their relationship to adult granulosa cell tumor remains to be determined.

Most Sertoli–Leydig cell tumors are seen in young patients (average age, 25 years) and they are relatively rare after menopause. Some are diagnosed during pregnancy.[578] These tend to exhibit prominent intercellular edema. Bilateral involvement is seen in less than 2% of cases. Cases have been reported in association with mature cystic teratoma.[656] Nearly half are accompanied by signs of androgen excess. This is manifested first by *defeminization* (amenorrhea, breast atrophy, loss of subcutaneous tissue deposits) and later by *masculinization* (clitoral hypertrophy, deepening of the voice, hirsutism). Usually prompt return of feminine characteristics follows excision of the tumor, but the manifestations of masculinization disappear more slowly.

Some Sertoli–Leydig cell tumors do not have demonstrable endocrine effect, whereas others are accompanied by secretion of estrogen or progesterone. The latter is often the case for pure Sertoli cell tumors.[657] It is opportune to mention again that the diagnosis of these neoplasms should be based on their morphologic appearance rather than on the nature of their hormonal manifestations. Curiously, some cases of Sertoli–Leydig cell tumor have been associated with serum elevation of alpha-fetoprotein[658–660]; this marker has been detected immunohistochemically in areas of hepatocytic differentiation[642] and in the more conventional Leydig and Sertoli cell-like component.

The prognosis of Sertoli–Leydig cell tumor, which is usually good, correlates with the stage and degree of differentiation of the tumor.[661,662] The overall incidence of clinical malignancy in one large series was 18%; all the well-differentiated tumors were benign, but 11% of those with intermediate differentiation, 59% of those with poor differentiation, and 19% of those with heterologous elements were malignant.[642] In one series of 28 cases of pure Sertoli cell tumor, there were two recurrences.[640] Conservative surgery is indicated in young women for Sertoli–Leydig cell tumors grossly confined to the ovary.[639,662]

Steroid Cell Tumor

A small group of ovarian tumors is composed entirely of cells with morphologic features indicative of steroid hormone secretion. These are manifested by an abundant eosinophilic or vacuolated cytoplasm that is often positive for fat stains and that, at the ultrastructural level, is shown to contain well-developed smooth endoplasmic reticulum and mitochondria with tubulovesicular cristae.[663] Normal steroid hormone-secreting cells can be of lutein (thecal or stromal), Leydig (hilus), and adrenal cortical type.[664] Theoretically, these tumors could arise from any of these sources. In the few cases in which Reinke crystalloids are found, the tumor can be categorized as **Leydig cell tumor**.[664–666] The exact origin of this tumor remains undecided; the descriptive terms **lipid**, **lipoid**, and—more recently—**steroid cell tumor** have therefore been proposed for the entire group, with the subcategory of Leydig cell tumor recognized for those tumors with Reinke crystalloids or arising in the hilus, with associated hilus cell hyperplasia.

Steroid cell tumors are usually unilateral and are composed of yellow or yellowish-brown nodules separated by fibrous trabeculae (Fig. 35.111). Microscopically, they are characterized by masses of large rounded or polyhedral cells with the morphologic and ultrastructural features previously described for their normal counterparts (Fig. 35.112). Immunohistochemically, there is reactivity for vimentin in three-fourths of cases, for keratin in one-half, and for actin in about one-third.[667] There is also consistent reactivity for inhibin and Melan-A.[668]

This neoplasm can occur at any age. Most are associated with a virilizing syndrome (with defeminization and amenorrhea), and a few cases meet the criteria for Cushing syndrome. Some of the tumors are biologically inactive, at least at the clinical level, and others are associated with estrogenic or progestogenic manifestations. A few cases have been associated with endometrioid carcinoma.[669] The incidence of clinical malignancy is approximately 25%.[670] Malignant tumors tend to be larger (7 cm in diameter or greater), with foci of necrosis and hemorrhage, and often exhibit nuclear atypia and mitotic activity.[670] Tumors containing Reinke crystalloids are almost invariably benign.[665]

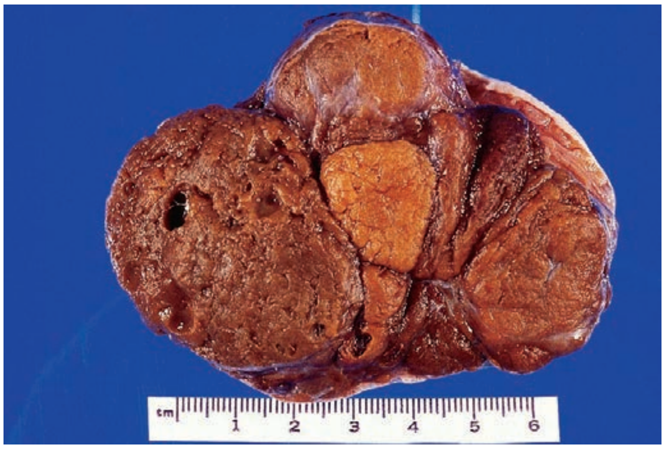

Figure 35.111 Cut Surface of Ovarian Steroid Cell Tumor. The deep brown color is reminiscent of a renal or thyroid oncocytoma.

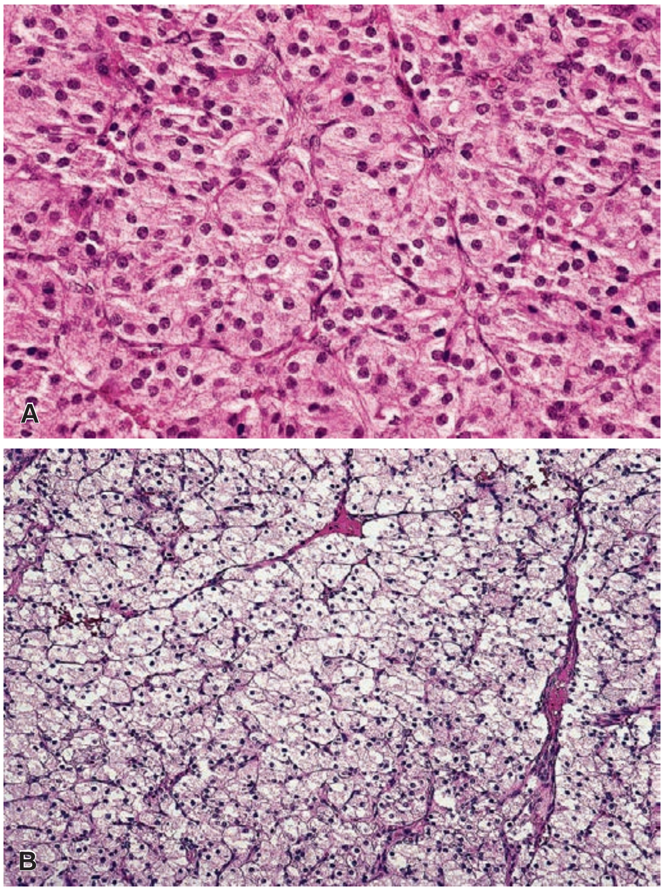

Figure 35.112 Two cases of steroid cell tumor showing acidophilic **(A)** and clear **(B)** appearances of the cytoplasm of the tumor cells.

Steroid cell tumors should be distinguished from lesions in which acquisition of cells with features of steroid hormone–producing cells occurs as a secondary event. These include luteinized granulosa cell tumor (particularly the juvenile type), fibrothecoma, and the relatively common finding of proliferation of non-neoplastic steroid cells that may be seen at the periphery of other tumors, such as struma ovarii, strumal carcinoid, epithelial tumors, and metastatic carcinoma.[671]

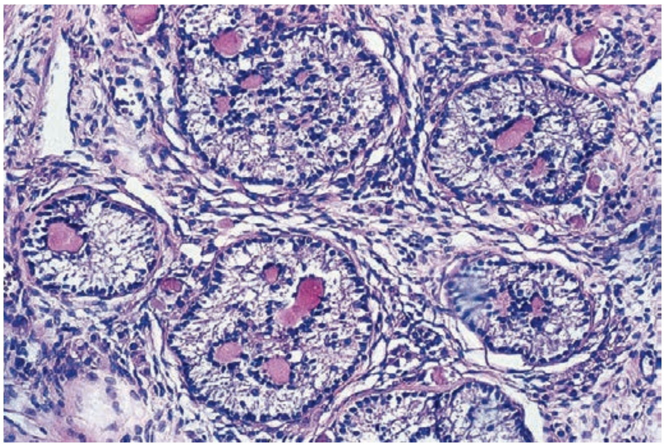

Figure 35.113 Sex Cord Tumor With Annular Tubules. The patient was affected by Peutz–Jeghers syndrome.

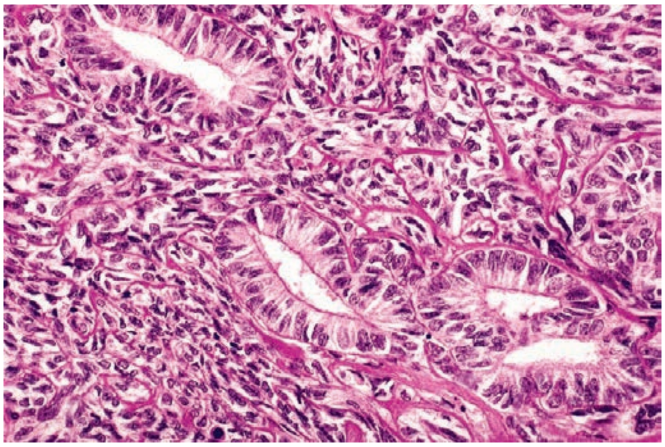

Figure 35.114 Wolffian Tumor of Ovary. Elongated glandular structures are admixed with solid foci composed of oval to spindle cells.

Other Types

Gynandroblastoma is the term used for the sex cord–stromal tumor composed of a mixture *in similar amounts* of clearly identifiable granulosa cell and Sertoli–Leydig cell elements.[672] When thus defined, this entity is extremely rare. On occasion the granulosa cell component is of the juvenile rather than the adult type.[673,674] Reported cases of this entity have been accompanied by androgenic, estrogenic, or no hormonal effects.[675,676] Examples of late recurrence following excision are on record.[677] Mutations in *DICER1* can be found in gynandroblastomas, in particular those where the granulosa cell component is of juvenile type.[678]

Sex cord tumor with annular tubules is a distinctive ovarian tumor that is associated in one-third of the cases with the Peutz–Jeghers syndrome.[679,680] This lesion combines features suggestive of a granulosa cell tumor with a pattern of growth reminiscent of Sertoli cells.[681] Its morphologic hallmark is the presence of simple and complex annular tubules containing eosinophilic hyaline bodies, often calcified (Fig. 35.113). The appearance is similar to that of gonadoblastoma, from which it differs because of the clinical/genetic background and the presence of a germ cell component in the latter.

The ambiguous or biphasic nature of the tumor cells is also apparent on ultrastructural examination: features consistent with granulosa cell or nonspecialized ovarian stroma[682,683] alternate with features indicative of Sertoli cell differentiation, notably the presence of Charcot–Bottcher filaments.[684] Symptoms suggestive of hyperestrinism have been described in approximately 50% of cases. Tumors associated with the Peutz–Jeghers syndrome are typically multifocal, bilateral, small (or even microscopic), calcified, and usually benign, although exceptions occur.[685] Those unassociated with the syndrome are unilateral, often large, and clinically malignant in approximately 22% of cases.[686,687]

It should be mentioned here that Peutz–Jeghers syndrome can be associated with other neoplasms of the female genital tract, such as other sex cord–stromal ovarian tumors,[688] mucinous ovarian tumors, and HPV-independent well-differentiated adenocarcinoma of the cervix of gastric type (adenoma malignum).

Wolffian tumor is the designation for the tumor entity first named *ovarian tumor of probable wolffian origin or female adnexal tumor of probable wolffian origin* (the latter designation reflecting its more frequent occurrence in the broad ligament, compared to the ovary).[689–691] It is thought to be of wolffian (mesonephric) derivation. Although it is not thought to be sex cord–stromal in nature, they are discussed here because of their resemblance to them and the fact that their immunophenotype overlaps with that of tumors in the sex cord-stromal category. Grossly, they may be either solid or solid and cystic. Microscopically, epithelial cells are seen growing in the form of cystic structures, solid or hollow tubules, and diffuse sheets (Fig. 35.114). The sieve-like appearance on low-power examination is a useful diagnostic feature. Conversely, the presence of a predominant spindle cell component can be confusing.[692] PAS-positive basement membranes are prominent around the epithelial aggregates. These tumors lack stromal cells of steroid hormone–secreting type and are unaccompanied by hormonal manifestations. Mucin stains are negative. Immunohistochemically, the tumor is positive for keratin (CK7 but not CK20), androgen receptor (three-fourths of cases), estrogen and progesterone receptors (one-fourth), inhibin (over half), FOXL2, calretinin (almost all), and vimentin (always). Surprisingly, given its putative wolffian origin, most cases are negative for GATA3.[693] It is negative for CEA. The behavior is generally benign, but a few have recurred or metastasized.[691,694,695]

Signet ring stromal tumor of the ovary is a very rare type but of great practical importance because of the fact that it can be easily mistaken for Krukenberg tumor. Some of the examples may be variants of sclerosing stromal tumor. The tumor cells are negative for keratin, PAS, and mucin. Their behavior is benign.[696]

Microcystic stromal tumor is the latest addition to the group of sex cord–stromal ovarian neoplasms.[697] It is usually unilateral and nonfunctioning. Microscopically, its most distinctive feature is the presence of small round to oval cystic spaces, in areas coalescing to form larger irregular channels, combined with lobulated cellular masses with intervening fibrous or fibrohyaline stroma. Mutations in β-catenin, with associated nuclear immunoreactivity, are a feature of this tumor.[698,699]

Sex cord–stromal tumor NOS (indeterminate or unclassified type) is a justifiable designation for ovarian tumors in which the cytologic and/or architectural features are consistent with a sex cord–stromal origin but which cannot be assigned to any specific category. These tumors are decidedly uncommon. Their behavior is similar to that of granulosa cell tumor and Sertoli–Leydig cell tumor, with a generally favorable prognosis when confined to the ovaries at presentation.[699,700]

Germ Cell–Sex Cord–Stromal Tumors

The most distinctive member of the group of tumors composed of a combination of germ cells and sex cord–stromal cells is **gonadoblastoma**.[701] This tumor occurs practically always in sexually abnormal individuals, most commonly affected by gonadal dysgenesis and carrying all or part of the Y chromosome (i.e. XY gonadal dysgenesis and XO-XY mosaicism but not XX gonadal dysgenesis). The testis-specific protein Y-encoded gene is the putative gene for the gonadoblastoma locus on the Y chromosome.[702]

The risk of neoplasia in these dysgenetic gonads is estimated to be 25%. However, gonadoblastomas have also been documented in phenotypically and chromosomally normal females, even during pregnancy.[703,704] They have also been seen in association with ataxia–telangiectasia.[705] It is often impossible to determine the nature of the gonad bearing the tumor. In some cases it has been identified as a streak and in others as a cryptorchid testis, but never as a normal ovary.

Approximately 36% of the tumors are bilateral. They are usually small, and many become apparent only on microscopic examination (Fig. 35.115).[706] The key microscopic feature is the admixture of primitive germ cells (resembling those of dysgerminoma) with sex cord–stromal cells resembling morphologically and immunohistochemically immature Sertoli and granulosa cells (Fig. 35.116).[707–709] Steroid hormone–producing cells may also be present, especially after puberty; their capacity for steroidogenesis has been demonstrated by their in vitro production of androgens and estrogens.[710] Hyalinization and calcification are common. The hyaline material reacts strongly with anti-laminin antibodies, indicating basement membrane deposition.[711]

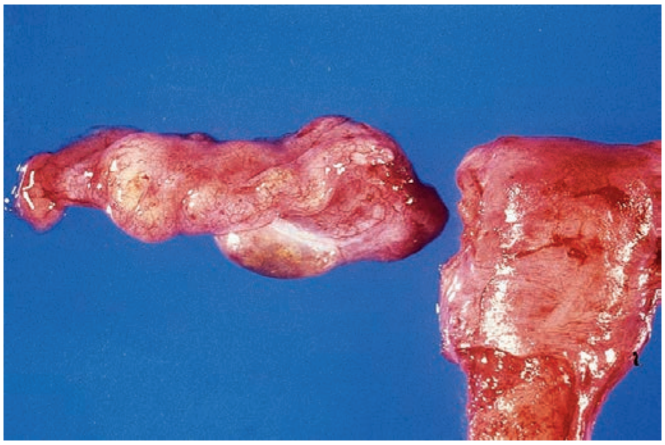

Figure 35.115 Streak gonad microscopically shown to contain gonadoblastoma. The tumor was barely apparent grossly.

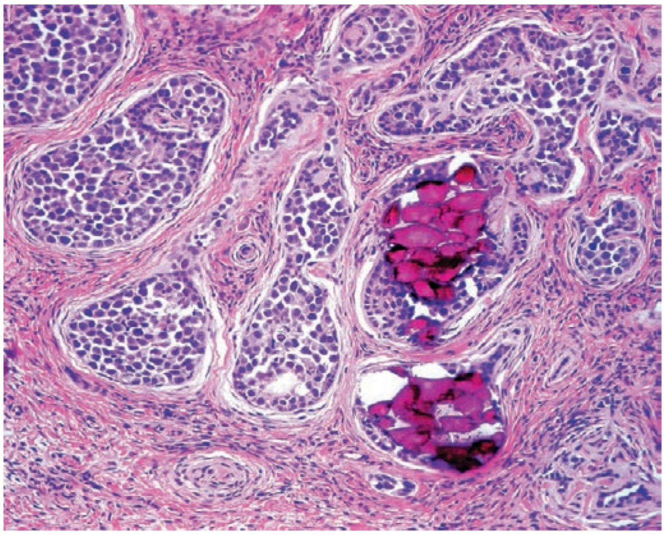

Figure 35.116 Ovarian Gonadoblastoma. Note the sharply outlined tumor nests and the heavy calcification.

An interesting analogy has been made between gonadoblastoma and intratubular germ cell neoplasia of the testis on the basis of the morphology and the immunohistochemical profile, the implication being that gonadoblastoma is an in situ germ cell malignancy arising in a dysgenetic gonad.[709]

The germ cell component of gonadoblastoma may overgrow the stromal elements and result in the formation of a germinoma (i.e. a tumor that would be diagnosed as a seminoma if arising in the testis or dysgerminoma if arising in the ovary) or, exceptionally, another type of germ cell tumor.[712,713] Only under these circumstances is the tumor endowed with a malignant potential. Much more unusual is the overgrowth of the sex cord–stromal component, which may acquire the features of a Sertoli cell tumor.[714]

Microscopic structures resembling gonadoblastoma and sex cord tumor with annular tubules are sometimes found incidentally in the ovaries of *normal* infants and children in association with follicular cysts; it has been suggested that they represent the precursor of these tumors.[715]

Rare *germ cell–sex cord–stromal tumors* not fulfilling the diagnostic criteria for gonadoblastoma have been described in genetically normal females,[716,506] some of them containing retiform structures.[717] The germ cell component of these tumors—like that of gonadoblastomas—is positive for PLAP, OCT4, and CD117.[718] These tumors can be hormonally active and clinically malignant.[719] Like gonadoblastoma, they can be accompanied by dysgerminoma or other germ cell tumors.

Tumors Not Specific to Ovary

Malignant Lymphoma and Leukemia

Secondary ovarian involvement by generalized lymphoma or leukemia is well recognized.[720,721] Much more rarely, malignant lymphoma involves the ovaries as the primary manifestation of the disease (Fig. 35.117).[721–725] This is also true for *granulocytic sarcoma*.[726,727]

Nearly all ovarian lymphomas are of non-Hodgkin type.[728] In children, Burkitt lymphomas predominate; in adults, most are diffuse large B-cell lymphomas.[728,729] Immunophenotypically, practically all cases are of B-cell nature.[728,730] In the series of Osborne and Robboy,[731]

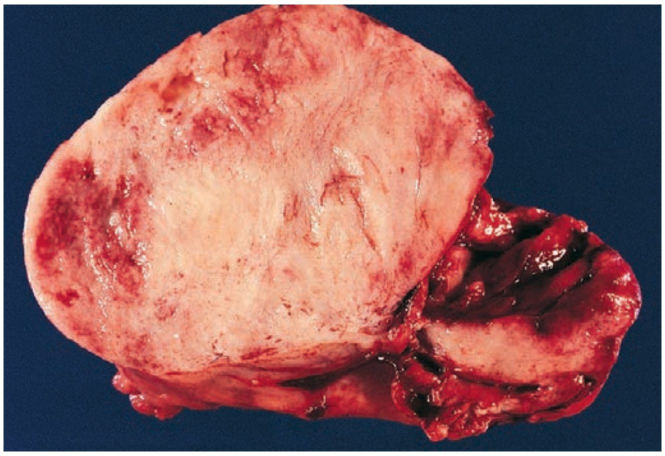

Figure 35.117 Malignant lymphoma of Burkitt type with massive ovarian involvement.

55% were bilateral, and 64% also involved extragonadal sites (usually the omentum, fallopian tubes, or lymph nodes); only 9 of their 42 patients survived more than 5 years, and 2 subsequently died of lymphoma.

Exceptionally, ovarian lymphoma has been found to coexist with a borderline serous tumor.[732]

Sarcoma

Primary sarcomas of the ovary are extremely rare. They need to be distinguished from undifferentiated carcinomas, carcinosarcomas/MMMTs, "sarcomatoid" forms of sex cord–stromal tumors, Krukenberg tumors associated with brisk stromal reaction, and cellular fibromas.

Fibrosarcomas are separated from cellular fibromas mainly on the basis of their mitotic activity (4 or more per 10 high-power fields) plus moderate to severe cytologic atypia; hemorrhage and necrosis are also common (see Figs. 35.94 and 35.95). They tend to be large, solid, and accompanied by adhesions. The clinical course is aggressive.[610] One case has been diagnosed in the context of the nevoid basal cell carcinoma syndrome.[733]

Endometrial (endometrioid) stromal sarcomas can present as primary ovarian neoplasms; they can closely simulate the pattern of growth of the diffuse type of granulosa tumor[734] but are recognized because of the presence of plump oval cells arranged around vessels of the spiral arteriole type.[735] Immunohistochemically, they are reactive for CD10 but negative for inhibin and FOXL2.

Müllerian adenosarcoma is discussed elsewhere, although it is probably more closely related to endometrial stromal sarcoma than to MMMT.

Other sarcomas of the adult ovary, all exceptionally rare, are *leiomyosarcoma*[736,737] (some of the myxoid type and some in patients with the nevoid basal cell carcinoma syndrome),[738,739] *chondrosarcoma*,[740] *osteosarcoma*,[741–743] *malignant peripheral nerve sheath tumor*,[744] *angiosarcoma*,[745] *rhabdomyosarcoma*,[746] *low-grade fibromyxoid sarcoma*,[747] and *Ewing sarcoma*.[748,749] The rhabdomyosarcomas are usually of the embryonal type, but they can also be of the alveolar variety[750]; a case has been reported in association with clear cell carcinoma.[751] The angiosarcomas show a wide morphologic spectrum and can be associated with mature cystic teratoma.[752,753]

The treatment of ovarian sarcoma is surgical excision ("cytoreduction") followed by chemotherapy.[754]

Other Primary Tumors

Hemangiomas of the ovary are usually small, found incidentally, unilateral, and cavernous in type.[755] Rarely, they are bilateral and/or associated with hemangiomas elsewhere in the body. Ovarian hemangiomas should be distinguished from the normal prominent hilar vasculature, lipid cell tumors having a prominent vascular component, and from the florid non-neoplastic vascular proliferation that sometimes accompanies the primitive neuroectodermal component of ovarian germ cell tumors.[439] Other types of vascular tumors that have been reported in the ovary are *infantile hemangioendothelioma*,[756] *lymphangioma* (which can be bilateral),[757] and *glomus tumor*.[758,759] *Leiomyomas* can exceptionally develop in the ovary, usually in association with uterine leiomyomas[760]; some are mitotically active and need to be distinguished from leiomyosarcomas.[761–763] The criteria for making this distinction are similar to those employed for their infinitely more common uterine counterparts (and just as frustrating).[758]

Isolated examples of ovarian myofibroblastoma,[764] epithelioid angiomyolipoma/PEComa,[765] nephroblastoma (Wilms tumor),[766] desmoplastic small cell tumor,[767] pheochromocytoma/paraganglioma,[768,769] and hydatidiform mole[770] have also been described. Adenomatoid tumor can occur in an intra- or juxta-ovarian location; it can simulate the appearance of yolk sac tumor,[771] and it can be predominantly composed of oxyphilic cells.[772]

The great majority of cases of *melanoma* involving the ovary are metastatic, but cases thought to be primary in the ovary have been described, the most convincing examples being those arising within a mature cystic teratoma or a struma ovarii.[773] Pancreatic-type solid and pseudopapillary neoplasm can also occur in the ovary.[774]

Metastatic Tumors

The ovary is a common site of involvement for metastases.[775–778] Approximately 7% of lesions presenting clinically as primary ovarian tumors are of metastatic origin. Over half are bilateral. The most common sources are stomach, large bowel, appendix, breast, uterus (corpus and cervix),[779] lung,[780,781] and skin (melanoma).[782–785] The difficult situation resulting from the simultaneous presence of carcinoma in ovary and uterus is discussed elsewhere. At the time when therapeutic oophorectomies were done in patients with breast carcinoma, it was not unusual to find small and sometimes microscopic (occult) metastases. Their pattern of growth could be either diffuse (with single file formations, suggestive of a lobular nature) or glandular, more in keeping with a ductal type. Immunoreactivity for GCDFP-15 and GATA3 is the rule, a fact of importance in the differential diagnosis with primary ovarian carcinoma, which is generally negative.[786,787] The reverse is true for WT1 and PAX8, which tend to be positive in ovarian carcinomas but negative in breast carcinoma.[161,788]

Adenocarcinomas of the large bowel are particularly important because of their relatively high frequency and their ability to simulate primary ovarian carcinomas, mainly of the mucinous and endometrioid types but sometimes also of the clear cell type (Fig. 35.118).[784,789–791] The primary tumors are usually advanced but sometimes are small and clinically occult.[792] The ovarian metastases tend to be cystic, well differentiated, mucin-producing, and associated with necrosis and hemorrhage. In some cases (particularly those of cecal origin), the ovarian metastases are associated with luteinization of the surrounding stroma, which may lead to masculinization and other endocrine changes.[793]

Features favoring metastasis from large bowel are bilaterality, surface involvement by tumor cells, infiltrative or nodular pattern of invasion, ovarian hilar involvement, single cell invasion, signet ring cells, garland and cribriform growth pattern, "dirty" necrosis, segmental destruction of glands, lack of squamous metaplasia, and vascular invasion (Fig. 35.119).[789,794–796] Features favoring a primary ovarian tumor are an expansile (pushing) pattern of invasion, a complex papillary architecture, size over 13 cm, a smooth external surface, and the presence of benign- and borderline-appearing foci.[795] This combination of primarily architectural features should allow the differential diagnosis to be made in the large majority of cases with the H&E sections. Unfortunately, exceptions to each and every one of these criteria exist.[797] Immunohistochemical stains can be of great assistance, although they also fall short of being pathognomonic. Metastatic large bowel carcinoma is characteristically CK7–/CK20+, CDX2+, and SATB2+. By contrast, primary ovarian mucinous carcinomas are nearly always CK7+ and variably CK20+, SATB2+, and CDX2+.[798–800] Hormone receptors are of no help, being negative in both metastatic carcinoma from the colon and the usual type of primary ovarian mucinous carcinoma.[801]

It should be realized that these distinctions apply specifically to the large bowel. Ovarian metastases from gastric, biliary, or pancreatic primaries have different phenotypic features (Fig. 35.120).[225,802–804] Of note, pancreaticobiliary adenocarcinomas often have bland foci

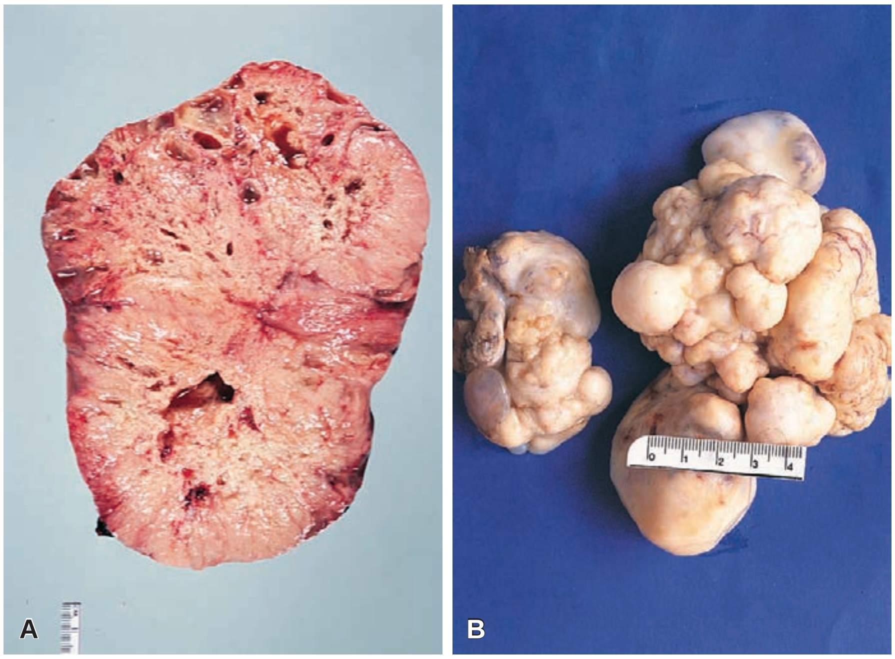

Figure 35.118 **A** and **B,** Colonic carcinoma metastatic to ovary. This may be misdiagnosed as a primary ovarian tumor both grossly and microscopically.

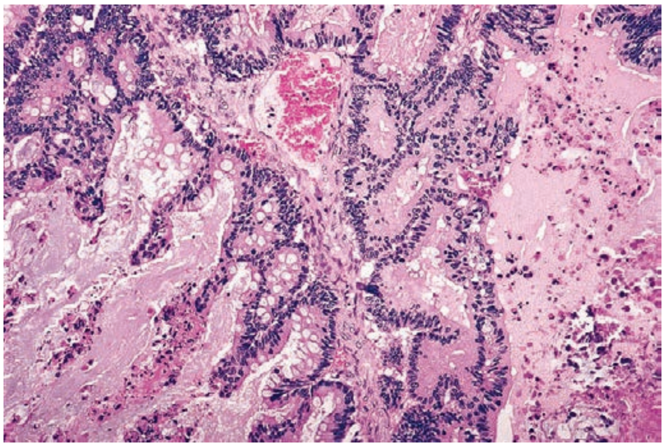

Figure 35.119 Colonic carcinoma metastatic to ovary.

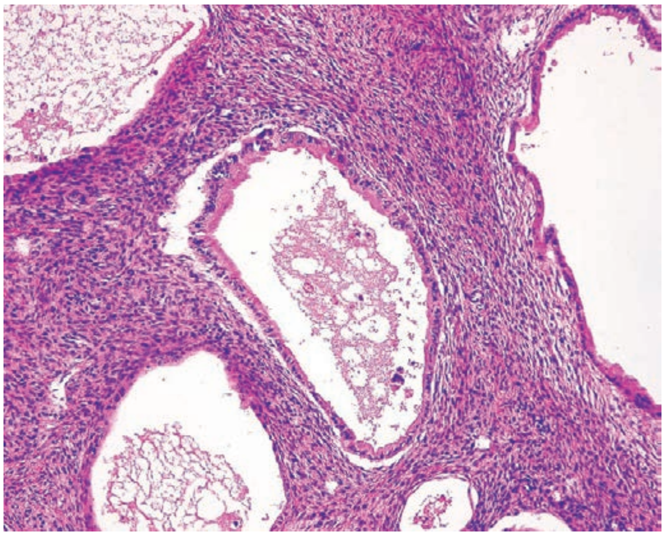

Figure 35.120 **Ovarian Metastasis From Pancreatic Adenocarcinoma.** As in the primary tumor, this ovarian metastasis shows the disparity between the extremely well-differentiated architecture and the high degree of nuclear atypia that is characteristic of pancreatobiliary neoplasms.

that simulate a benign or borderline ovarian mucinous tumor. The peculiar situation concerning the relationship of ovarian mucinous tumors and pseudomyxoma peritonei has been mentioned earlier in this chapter. Briefly, the current consensus—based on a combination of clinical, morphologic, immunohistochemical, and molecular observations—is that the overwhelming majority of these tumors are primary appendiceal neoplasms that have implanted on the peritoneal surface and on the ovaries.[805,806] However, that may not be true for all cases (e.g. the rare appendiceal-type ovarian mucinous adenocarcinomas arising from benign cystic teratomas).[482]

Metastatic carcinoid tumors to the ovary are discussed elsewhere. Small cell (neuroendocrine) carcinomas from the lung, gastrointestinal tract, thymus, and other sites can metastasize to the ovary; these should be distinguished from both the hypercalcemic and the pulmonary type of primary ovarian small cell carcinoma,[807] the latter being a more difficult task.

The eponym **Krukenberg tumor** is used to designate an ovarian neoplasm, usually bilateral and nearly always of metastatic origin, characterized grossly by moderate solid multinodular enlargement of the ovaries and microscopically by a diffuse infiltration by signet ring cells containing abundant neutral and acidic (sialo) mucins[808–811] (Figs. 35.121 and 35.122). Tumor emboli are found in over half of the cases.[812] Marked stromal proliferation with a storiform pattern of growth and a variable degree of luteinization are common and may obscure the diagnosis.[811] Another difficult problem is represented by the variant of this tumor referred to as *tubular*, in which a prominent tubular pattern, stromal luteinization, and

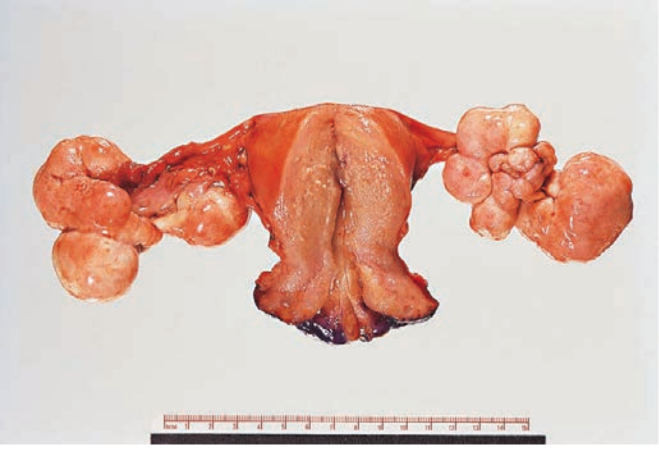

Figure 35.121 **Typical Gross Appearance of Krukenberg Tumors of Ovary.** The involvement is bilateral and the tumors are characterized by a multinodular outer appearance. (Courtesy of Dr. RA Cooke, Brisbane, Australia; from Cooke RA, Stewart B. *Colour Atlas of Anatomical Pathology*. Edinburgh: Churchill Livingstone; 2004.)

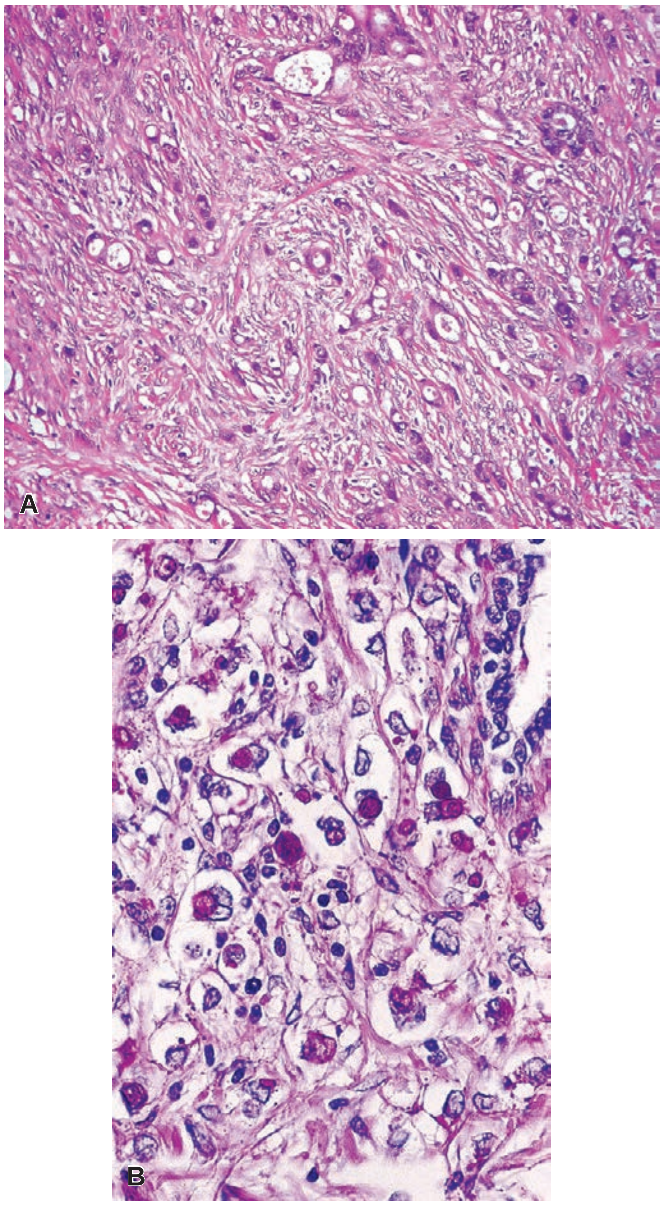

Figure 35.122 **Krukenberg Tumor of Ovary. A,** Microscopic appearance. Numerous signet ring cells are present in a highly fibrous stroma, either individually or in small nests. **B,** Presence of intracellular mucin evidenced by Meyer mucicarmine stain.

occasional associated virilization may lead to a mistaken diagnosis of Sertoli–Leydig cell tumor (Fig. 35.123)[812]; the presence of typical mucin-positive signet ring cells should point toward the correct diagnosis.

Most examples of Krukenberg tumors occur after the age of 40 years, but younger patients can also be affected. In the latter instance, a mistaken diagnosis of granulosa cell tumor or steroid cell tumor may be made.

The usual primary sources of Krukenberg tumor are stomach, large bowel, appendix, and breast (Fig. 35.124).[812–815] Of these, diffuse gastric carcinoma ("linitis plastic") used to be the most common, but at present there is a preponderance of cases originating from the breast, at least in the United States. The ovarian deposits can be accompanied by retroperitoneal lymph node metastases and peritoneal implants. A rarer phenomenon is ovarian metastasis from gastric carcinoma of intestinal type.[816]

Exceptionally, an extra-ovarian primary tumor is not found at autopsy in a patient harboring a Krukenberg tumor. In such an instance, the lesion is assumed to be primary in the ovary.[817] Before such an occurrence is accepted, a meticulous study of the gastrointestinal tract, breast, and other organs should be carried out.[812] It should be emphasized here that the diagnosis of Krukenberg tumor requires the histochemical identification of intracytoplasmic mucin, and the immunohistochemical detection of epithelial markers, inasmuch as mucin negative signet ring cells are occasionally seen in other ovarian conditions.[818]

Other tumors that can metastasize to the ovary and give rise to difficult diagnostic problems are pancreatobiliary ductal adenocarcinoma (which can simulate primary ovarian mucinous tumors and which can arise in the pancreas, gallbladder or extrahepatic or intrahepatic bile ducts),[819–822] pancreatic acinar cell carcinoma,[823] renal cell carcinoma (which mimics ovarian clear cell adenocarcinoma),[824,825] carcinoma of the renal pelvis,[826] thyroid carcinoma (which can be confused with struma ovarii),[827] hepatocellular carcinoma and hepatoblastoma (not to be mistaken for hepatoid yolk sac tumor or hepatoid carcinoma, all of which are Hep Par1 positive[828]),[829,830] intra-abdominal desmoplastic small cell tumor (of which the ovary can be the only manifestation),[831,832] and a variety of sarcomas, including rhabdomyosarcoma,[777] leiomyosarcoma, osteosarcoma,[833] gastrointestinal stromal tumor (GIST),[834] soft tissue–type clear cell sarcoma,[835] and chordoma.[778,836,837] We have also seen ovarian metastases from malignant thymoma.

Malignant melanomas are usually easy to recognize because of their pigmentation, nodular pattern of growth, and cytologic features; however, some can be confused with primary ovarian tumors (particularly juvenile granulosa cell tumor and the hypercalcemic type of small cell carcinoma) because of their tendency to form follicle-like spaces (Figs. 35.125 and 35.126).[785] Positivity for S-100 protein, SOX-10, Melan-A, and HMB-45 should remove whatever doubts may remain after examination of H&E-stained sections.[838] Metastatic melanoma should be distinguished from the much rarer primary ovarian melanoma.

Not surprisingly, carcinoma metastatic to the ovary is generally associated with a very poor prognosis.

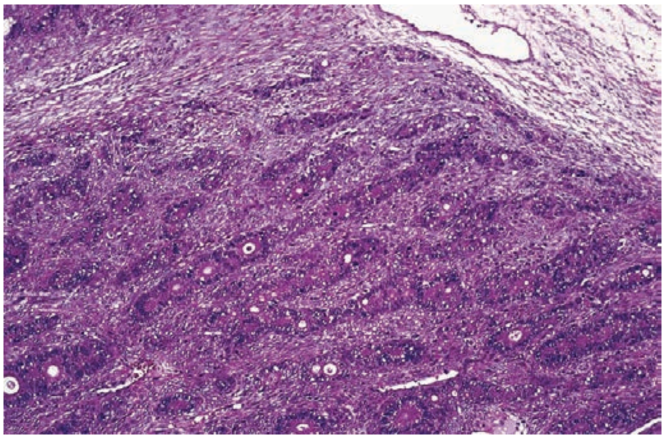

Figure 35.123 Tubular variant of Krukenberg cell tumor.

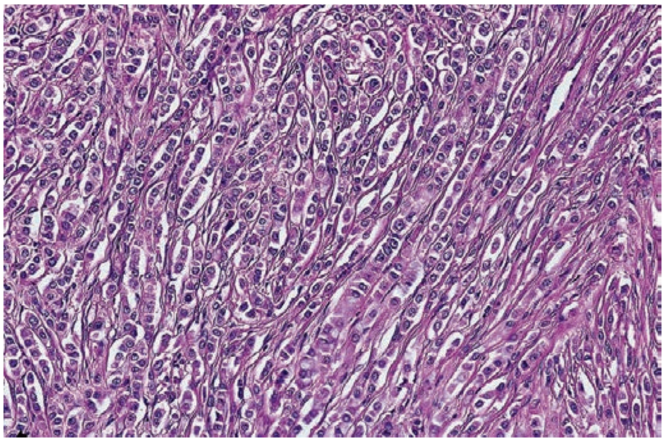

Figure 35.124 Ovarian metastasis of lobular carcinoma of breast.

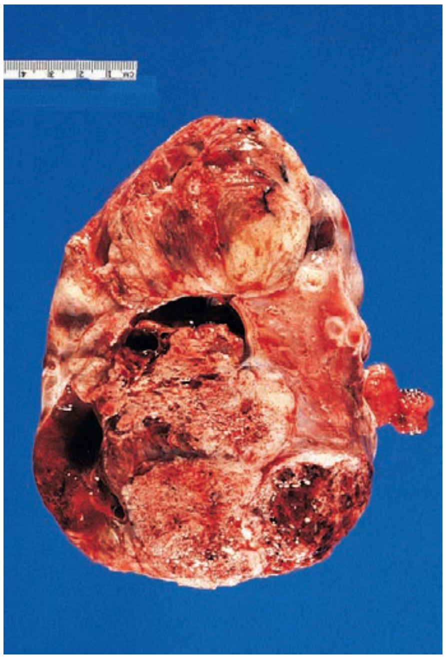

Figure 35.125 Gross appearance of ovarian metastasis of a malignant melanoma.

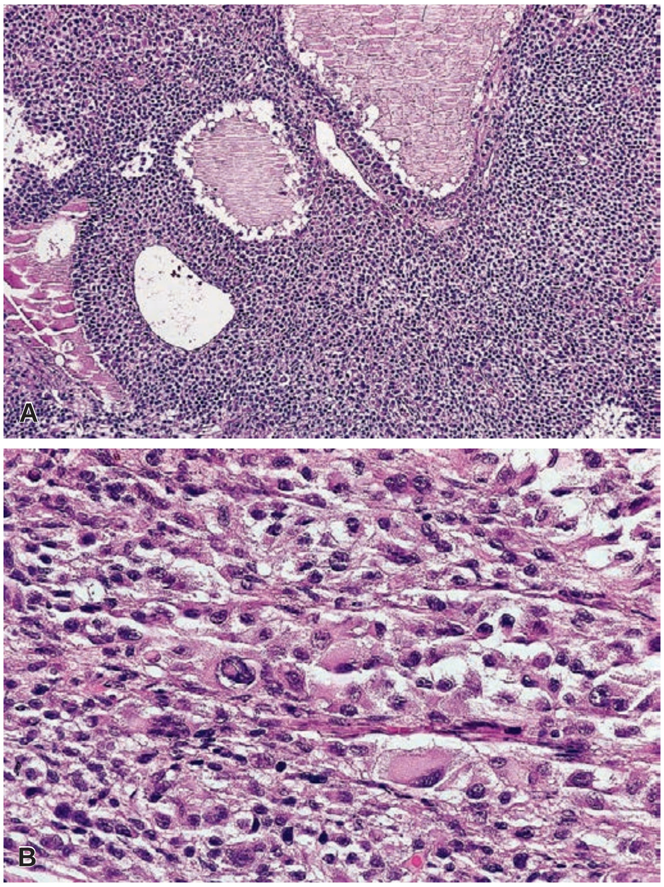

Figure 35.126 **A** and **B,** Low- and high-power appearances of ovarian metastasis from malignant melanoma. The follicle-like formations seen in **A** may result in a misdiagnosis of juvenile granulosa cell tumor or hypercalcemic-type small cell carcinoma.

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